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P/00/009
Regulation 3.2

AUSTRALIA

Patents Act 1990

PROVISIONAL SPECIFICATION

Invention Title: "PEPTIDE TURN MIMETICS"

The invention is described in the following statement:

TITLE

"PEPTIDE TURN MIMETICS'

FIELD OF THE INVENTION

THIS INVENTION relates to new compounds designed to be peptide turn mimetics. Such compounds are used to reproduce structural and functional elements of reverse turns contained in bio-active peptide sequences principally in order to develop novel pharmaceuticals with increased binding affinity, selectivity, stability and/or oral bioavailability compared to the bio-active peptide.

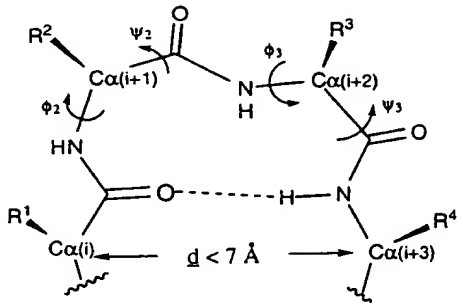
BACKGROUND OF THE INVENTION

Reverse turns (beta and gamma turns and beta buldges) are localised on the protein surface[Kuntz, 1972 #134] and are of importance in protein interactions [Rose, 1985 #135; Chalmers, 1995 #236] (and references contained therein). In addition reverse turns are important structures of peptide hormones and other biologically active peptides and cyclic peptides.[Olson, 1993 #219; Giannis, 1993 #115; Kessler, 1995 #65]

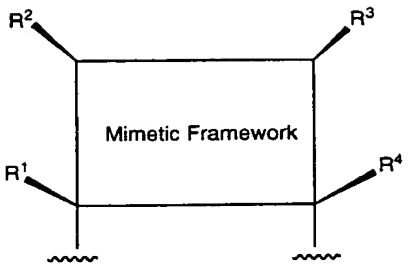
Peptide mimetics and peptide turn mimetics have as their object the replacement of a peptide sequence (a peptide turn) with a new compound which retains the elements essential for biological activity, thereby enabling or facilitating the development of novel pharmaceuticals devoid of the inherent problems of peptides - namely flexibility and poor pharmacodynamics. The essential elements for biological activity are thought to be the peptide sidechain groups[Farmer, 1982 #226; Ball, 1990 #213], therefore a peptide mimetic should include the side chain groups to have the best chance of retaining biological activity. A peptide mimetic may then take the form of a framework for displaying sidechain groups in an appropriate arrangement.

The majority of reverse turns are beta turns. The generally accepted definition of the beta turn is a sequence of four residues where the distance between the alpha carbons of residue (i) and residue (i+3) (defined as d) is less than 7Å, and the central residues (i+1, i+2) are non-helical.[Lewis, 1973 #127] The general structure is shown below and includes the phi (ϕ) and psi (ψ) backbone dihedral angles that are used to describe the conformation of the peptide backbone. A schematic conversion of the beta turn to a beta

turn mimetic is also shown - the peptide backbone is replaced by an undefined framework.

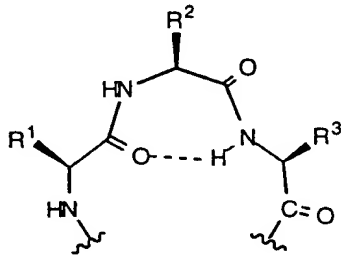


General structure of a hydrogen bonded β-turn. The four backbone dihedral angles traditionally used in turn classification are indicated, and also the position of the 7Å upper distance cutoff for d used for the definition of β-turns.



A schematic representation of a beta turn mimetic - the peptide backbone has been replaced by an alternative chemical framework, represented here by a rectangle

The gamma turn is generally defined by the presence of a hydrogen bond between C=O (i) and N-H (i+2) to form a pseudo seven membered ring as illustrated below.[Milner-White, 1988 #130] Where the equivalent hydrogen bond is present in a beta turn a pseudo ten membered ring is formed.



General structure of a γ-turn, defined by the presence of a hydrogen bond between the C=O of (i) and the N-H of (i+2), as indicated.

The chemical synthesis of a framework having four independent chiral groups each with a wide range of possible functionality (for example a beta turn mimetic) is a very significant synthetic challenge [Nakanishi, 1996 #225] as illustrated by the the fact that most proposed beta turn mimetics either do not provide for the incorporation of any sidechain functionality, or provide for a limited range of functionality, and at a limited

number of positions. Reference may be made to reviews by Ball and by Hölzemann for illustration of these points [Hölzemann, 1991 #399; Hölzemann, 1991 #400; Ball, 1990 #213]. In the case of mimetics that do provide for the incorporation of functionality the synthesis may be complex and lengthy, and most seriously may require a different synthetic method for different sidechain sequences (i.e. the synthetic method is not generic). For example in the work of Callahan, Huffman and Newlander on gamma turn mimetics the synthetic method varied depending on the sidechain sequence required - a 10 step sequence for a Gly-Phe-Leu mimetic, 13 steps for Phe-Gly-Val and 21 steps for Ala-Phe-Ala [Huffman, 1988 #18; Newlander, 1993 #35; Callahan, 1992 #3]. Given that the possible combinations of three residue sequences of the 20 natural amino acids is 8000 (20x20x20), and 160,000 for the four residue beta turn sequence, such non-generic methods are of limited use. The methods were further hampered by a lack of chiral control.

In the development of peptide turn mimetics a further important issue is the reproduction of the variety of different turn conformations, particularly of the beta turn. Several different methods of describing turn conformation have been proposed, the traditional method having several turn types based on the backbone dihedral angles of the (i+1) and (i+2) residues i.e. I, I', II, II', III, III', IV, V, VIa, VIb, VII and VIII, with even this diversity of types being insufficient to adequately describe turn conformations.[Richardson, 1981 #128; Wilmont, 1990 #147; Ball, 1993 #4] No single mimetic framework can accurately mimic this diversity of turns.

The problems encountered in the development of peptide turn mimetic syntheses are discussed in a review by Kahn [Kahn, 1993 #64] and reference may also be made to a review article entitled "Design of Peptidomimetics" [Nakanishi, 1996 #225] which discusses aspects of mimetic design and developments regarding peptide mimetics.

The uses of reverse turn mimetics (and peptides or other compounds containing reverse turn mimetics) in drug development have been described in the art, notably in publications by Kahn and co-workers [Kahn, 1996 #252; Qabar, 1996 #71; Nakanishi, 1996 #225] and references contained therein. An important example of the application of

reverse turn mimetics is the production of mimetics of known biologically active cyclic peptides (typically penta- or hexapeptides), as illustrated by Hirschmann and co-workers with β-D-glucose based mimetics.[Hirschmann, 1992 #54; Hirschmann, 1993 #224]

Other beta turn mimetics having biological activity are known in the art. For example U.S. Patent 4535169 discloses a method for the synthesis of beta turn mimetics which can incorporate a functional substitution for the (i+3) sidechain, and Krystenansky et al. disclose a leucine enkephalin mimetic based on this method which had analgesic activity one third the potency of morphine [Krstenansky, 1982 #248].

Reference may also be made to U.S. Patents 5475085 and 5618914 and International Publication WO96/22304 (all Kahn, M) which describe methods for the synthesis of a range of reverse turn mimetics. These mimetics are all produced by a modular synthesis technique (that may be applied to solid phase synthesis) which involves amino acid derivatives and various dipeptide azetidinones synthesised by a variety of techniques. An important common step in all of the syntheses of these mimetics is the cyclisation reaction which involves the azetidinone as activated ester component. Conformational variation is introduced to these mimetics by the inclusion of a variable component ("X") in the ring of the cyclic turn mimetics. It should be noted that with two exceptions (the parent mimetics which have X=NH and have a ten or eleven membered ring) the beta turn mimetics produced by these methods have ring sizes of twelve members and above. Such large rings allow many conformations with $\underline{d}$>7Å, the mimetic conformations are therefore biased away from the accepted definition of a beta turn ($\underline{d}$ less than 7Å), or more importantly the conformations are biased away from the most common reverse turn conformations which have $\underline{d}$ in the range of 4.5Å to 6Å [Rose, 1985 #135; Gardner, 1993 #52]. Enkephalin mimetics have been made [Gardner, 1993 #52] and also mimetics of a loop of CD4 that inhibit binding of HIV gp120 and infection of human lymphocytes [Chen, 1992 #48]. The synthetic methods described for the majority of these mimetics appear to be limited with respect to the possible functionality at the (i) and (i+1) positions, and indeed no mimetic with any functionality at the (i+1) position (other than -H) appears to have been described at this time.

Reference may also be made to International Publication WO97/15577 (Kahn, M) which describes the synthesis of bicyclic reverse turn mimetics and chemical libraries containing such reverse turn mimetics. While concise, the synthetic methods do not provide for control of chirality at all positions, and the degree of sidechain function generality is questionable at two positions. Furthermore the structure of the mimetics means they are not able to be easily incorporated in a peptide sequence.

Reference may also be made to Virgilio et al. [Valle, 1989 #203; Virgilio, 1994 #184; Virgilio, 1996 #185] which incorporate functionality at the (i+1), (i+2) and (i+3) positions (not the (i) position) but do not allow for incorporation of the mimetic in a peptide sequence (i.e. no amino and carboxy terminal groups are present).

Reference may also be made to International Publication WO95/25120 which describes the use of turn mimetics in the synthesis of peptide vaccines for generating a protective immune response in warm blooded animals.

In the methods and mimetics of the aforementioned references several common problems are evident: limited numbers of sidechains are able to be reproduced, there is limited control of chirality in the syntheses and a limited range of sidechain functions could be included. In addition many of the syntheses of turn mimetics described are relatively long and complex, even when not all the sidechain functions are included, for example the syntheses of certain enkephalin mimetics were in the range of approximately 15 to 21 steps [Gardner, 1993 #52].

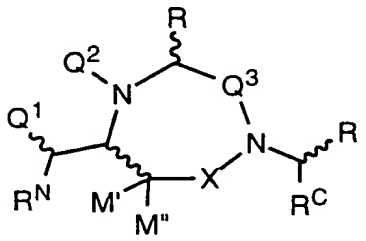
OBJECT OF THE INVENTION

It is therefore the object of the invention to provide novel compounds useful as conformationally constrained mimetics of biologically active peptide and protein reverse turns (i.e. reverse turn mimetics) that can display a wide range of sidechain functions at all sidechain positions, can be incorporated in a peptide sequence, and can be readily synthesised.

SUMMARY OF THE INVENTION

This invention describes novel compounds designed to be reverse turn mimetics, and methods for their synthesis. The compounds of the invention have the general

structure **X**, or in a preferred embodiment the general structures **I-VI** (which are subsets of the general structure **X**; see below and Figures 1 and 2 on the attached sheets; the structures are fully described in the detailed description following this summary).



X

It has now been discovered, unexpectedly, that B-allyldialkylboranes (e.g. **Rg1a-i**, Fig. 3) react with imines **3** (Scheme 1) to give the novel allyl amines **4a-d** with a very high degree of chemo- and stereoselectivity. In contrast to these good results, allylation with the related B-allyldialkoxyboranes (e.g. **Rg1j**, Fig 3) or allylcopper or allylzinc reagents gave inferior results with racemisation and reaction at other functional groups. It has also been discovered, unexpectedly, that boron enolates (e.g. **Rg2**, Fig. 4) react with imines **3** to give compounds **5a-d**. The reaction of imines **3** to form compounds **4a-d** and the related compounds **5a-d** forms the basis of the synthesis of all the compounds of the invention, and hence the invention. Thus the allyl amines **4a-d** and the related compounds **5a-d** are suprisingly valuable intermediates for the synthesis of reverse turn mimetics, enabling the synthesis of the significant variety of novel reverse turn mimetics of the invention (having the general structure **X**), by the variety of different pathways described herein. All the mimetic systems of the invention can be incorporated into peptide sequences, or if required the amino and/or carboxy termini can be omitted from the mimetic.

As described above, there is a need for a wide range of different mimetics to better reproduce the wide range of conformations found in native reverse turns. The turn mimetics of the invention have a large variety of novel ring structures, each of these therefore having novel conformational characteristics. Furthermore, the structure and

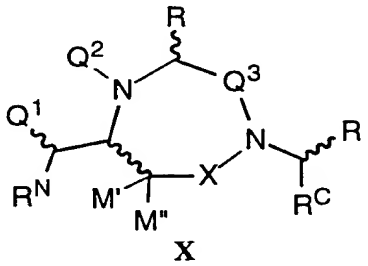
ring sizes of many of the turn mimetics make them well suited to the reproduction of the geometry of the more common native reverse turn conformations (with d of 4.5Å to 6Å).

The synthetic methods described are generally superior to the prior art in terms of the capacity to include a wide range of side chain functions, in all the sidechain positions, without significant changes in the synthetic method; that is, the methods are more truly *generic*. In addition, the control of chirality in the synthesis of the mimetics of the invention is generally superior to the prior art - an important consideration in the elucidation of structure-activity relationships and the development of novel pharmaceuticals as diastereomeric mixtures may be impractical or impossible to separate on a commercial basis.

The invention also includes all novel intermediates used in the preparation of the mimetics: **4-9(a-d)**, Scheme 1; **10-11**, Scheme 2; **12-13**, Scheme 3; **14-16**, Scheme 4; **18-19**, Scheme 5; **20-21**, Scheme 6; **23-24**, Scheme 7; **25-27(a-d)**, **28**, Scheme 8; **29-30**, Scheme 11; **31-36**, Scheme 12; **37(a-c)**, **38-40**, Scheme 13; **45-48**, Scheme 15.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the invention have the general structure **X**, shown below and defined as follows:



X

	X	Y
(i)	-CH(M)-	C(O)
(ii)	-C(O)-	CH_2
(iii)	-CH(Q^4)CH_2-	C(O)
(iv)	-CH(Q^4)C(O)-	CH_2

Q^1=R and Q^2=Z; alternatively there is a cyclisation from Q^1 to Q^2 and then in preferred embodiments of the invention Q^1Q^2 = -CH(R)C(O)- or -CH_2CH(R)C(O)- or -CH_2CH_2CH(R)C(O)-. Q^1Q^2 can also be: -CH(R)CH_2- or -CH_2CH(R)CH_2- or -CH_2CH_2CH(R)CH_2- or -CH_2CH(R)- or -CH(R)CH_2CH_2- or -CH_2CH(R)CH_2CH_2- or -CH(R)CH_2C(O)- or -CH_2CH(R)CH_2C(O)-

Q^4=M and Q^3=Y or -C(O)NHCH(R)Y or -C(O)ENHCH(R)Y; or alternatively Q^3=C(O)N(Q^4)CH(R)Y and Q^4 is a covalent bond from the X group to the nitrogen atom in Q^3 (a cyclisation forming a bicyclic ring system).

E=-$(NHCH(R)C(O))_n$- where n = 0, 1, 2, 3, 4.. etc. E is therefore a loop of n amino acids which are linked in a cycle by the rest of the mimetic system. The loop may also incorporate non-alpha amino acids, alpha dialkyl amino acids or any other amino acid which confers favourable properties on the mimetic system, for example increased binding affinity, or ease of detection, identification or purification. The invention, when used with such larger loops, is functioning as a covalent hydrogen bond mimic (another aspect of the invention), as described by Arrhenius et al. [Arrhenius, 1987 #181].

Preferred embodiments of the invention are the structures **I-VI**, as illustrated in Figures 1 and 2 and defined in the following table:

Table 1

Mimetic	Q^1	Q^2	Q^3	Q^4
I	R	Z	Y	-
II	R	Z	C(O)NHCH(R)Y	M
III	R	Z	C(O)NHCH(R)C(O)-NHCH(R)Y	M
IV	R	Z	C(O)N(Q^4)CH(R)Y	Q^3
V	CH(R)C(O)Q^2	Q^1	Y	M
VI	CH_2CH(R)C(O)Q^2	Q^1	Y	M

Recursive entries of Q groups in Table 1 indicate a cyclisation - thus mimetics **V** and **VI** have a cyclisation between Q^1 and Q^2, and mimetic **VI** has a cyclisation between Q^3 and Q^4. In the above Table the groups Q^1-Q^4 and X and Y are as previously defined, and the other groups are defined as follows:

R^1 to R^5 and other R groups unless otherwise indicated, are amino acid side chain groups, each independently chosen and therefore the same or different (two separate R groups in the same mimetic do not require a different suffix to indicate that they are independently chosen and can be the same or different). The definition of "amino acid side chain group" as used in this document is the same as the definition of "amino acid side chain moiety or derivative" as described in International Publication WO97/15577,

pages 7-9 (Kahn, M), incorporated herein by reference. Amino acid side chain groups typically correspond to, but are not limited to, those found in natural amino acids. Thus for glycine R=hydrogen; for alanine R=methyl; for phenylalanine R=-CH_2Ph; for valine R=-$CH(CH_3)_2$; for leucine R=-$CH_2CH(CH_3)_2$ etc.

Z is normally hydrogen, methyl, ethyl, formyl or acetyl, and may alternatively be R or -CH_2R or -C(O)R where R is an amino acid side chain group. For **II**, Z cannot be hydrogen due to compound instability.

R^C is the carboxy terminal part of the mimetic, typically -C(O)Pg(C) or alternatively hydrogen or an amino acid side chain group R or -CH_2R.

Pg(C) is a protecting group for carboxylic acid, typically including, but not limited to: benzyl, methyl, ethyl, t-butyl, allyl and fluorenyl methyl esters, easily removable amides, or alternatively an appropriate cleavable linker to a solid phase support, or such a support itself, or alternatively hydrogen or R or -C(O)R where R is an amino acid side chain group, or alternatively part or all of the remaining C-terminal portion of the mimetic system as described below.

R^N is the amino terminal part of the mimetic, typically -N(Z')Pg(A), alternatively hydrogen or an amino acid side chain group R or -CH_2R or -CH_2CH_2R.

Z' is normally hydrogen, alternatively methyl (to mimic an N-methyl amino acid residue at position (i)), or part of a cyclic amino acid side chain group joined to R^1 (for example to mimic a proline residue at position (i)).

Pg(A) is a protecting group for amine, typically including, but not limited to: Boc, Cbz, Fmoc, Alloc, trityl; or alternatively an appropriate cleavable linker to a solid phase support, or such a support itself, or alternatively hydrogen or R or -C(O)R where R is an amino acid side chain group, or alternatively part or all of the remaining N-terminal portion of the mimetic system, as described below.

M, M', M" are normally hydrogen, alternatively one or more may be C_1-C_4 alkyl (preferred methyl), chloro, C_1-C_4 alkoxy (preferred methoxy), or other small substituent.

W is -CH_2- (generally when Pg(A) is acyl) or -C(O)- (generally when Pg(A) is not acyl) or null (omit W).

The compounds of this invention have been designed to allow for incorporation in a peptide or protein chain, or for covalent attachment to any molecule or group that may be useful for the enhancement of the biological activity, or other property, of the reverse turn mimetic. Thus the term "remaining C- or N-terminal portion of the mimetic" is any group, molecule, linker, support, peptide, protein, nucleoside, glycoside or combination of these. Typically such remaining portions would be peptides or combinations of peptides and other mimetics, or compounds to facilitate detection or identification, or to improve the pharmacodynamics, of the mimetic system.

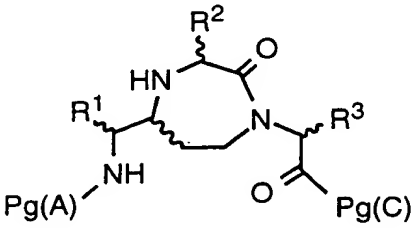
In addition, any R group (an amino acid side chain group) may serve as an attachment point to a solid support, or to a linker to a solid support, or as a covalent attachment point for another molecule that may be useful for the enhancement of the biological activity, or other property, of the mimetic, as described above for the remaining C- or N-terminal portions of the mimetic.

The term "cleavable linker" and "solid phase support" are as defined in International Publication WO97/1557

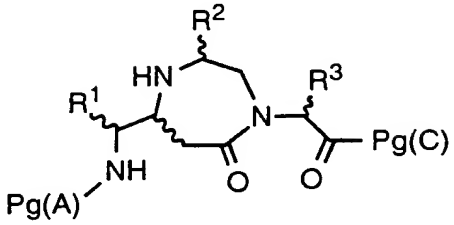
The use of a wavy line at chiral centres in the general structures **X** and **I-VI** and in the other structures in the Figures and Schemes indicates that the centre may be in either the R or S configuration, or be a mixture in any proportion of the R and S configurations. In most circumstances it is preferable to avoid mixtures of configurations unless the intention is to provide a mixture of diastereomers for example for the purpose of more efficient screening or for synthetic expediency. Chirality at the amino acid side chain positions in the compounds of the invention (e.g. R^1 to R^4) is controlled by the use of chiral starting materials (L or D amino acids) and the avoidance of synthetic conditions which cause racemisation. The configuration at chiral centres formed in the mimetic synthesis is dependent on several factors and can be controlled in several cases, but in other cases mixtures of diastereomers will result, which can potentially be separated by physical means.

Examples of preferred embodiments of the mimetics

γ-Turn mimetics **I(i)a**, **I(ii)a** (M, M', M", Z and Z' = hydrogen):

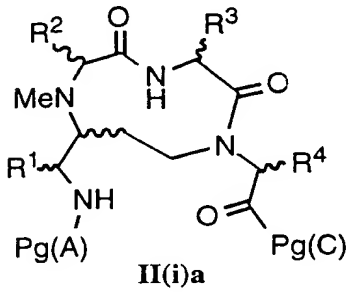


I(i)a

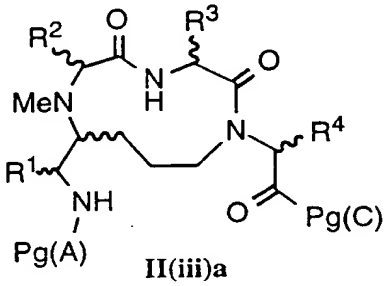


I(ii)a

β-Turn mimetics **II(i)a**, **II(iii)a** (M, M', M" and Z' = hydrogen, Z = Me):

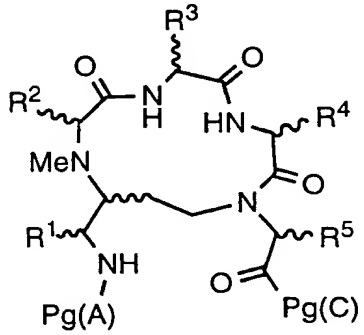


II(i)a

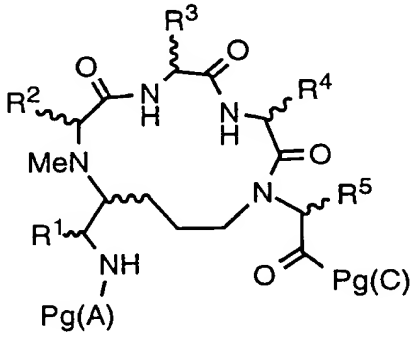


II(iii)a

β-Bulge mimetics **III(i)a**, **III(iii)a** (M, M', M" and Z' = hydrogen, Z = Me):

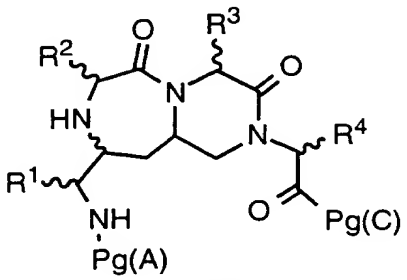


III(i)a

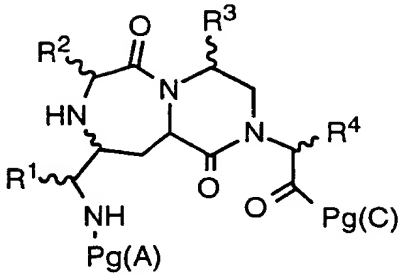


III(iii)a

Bicyclic β-turn mimetics **IV(i)a, IV(ii)a** (M, M', M", Z and Z' = hydrogen):

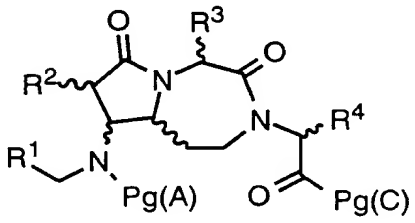


IV(i)a

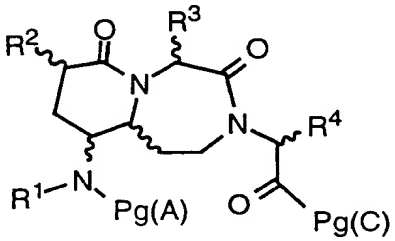


IV(ii)a

Bicyclic β-turn mimetics **V(i)a, VI(i)a** (M, M'and M" = hydrogen; W = CH_2)



V(i)a

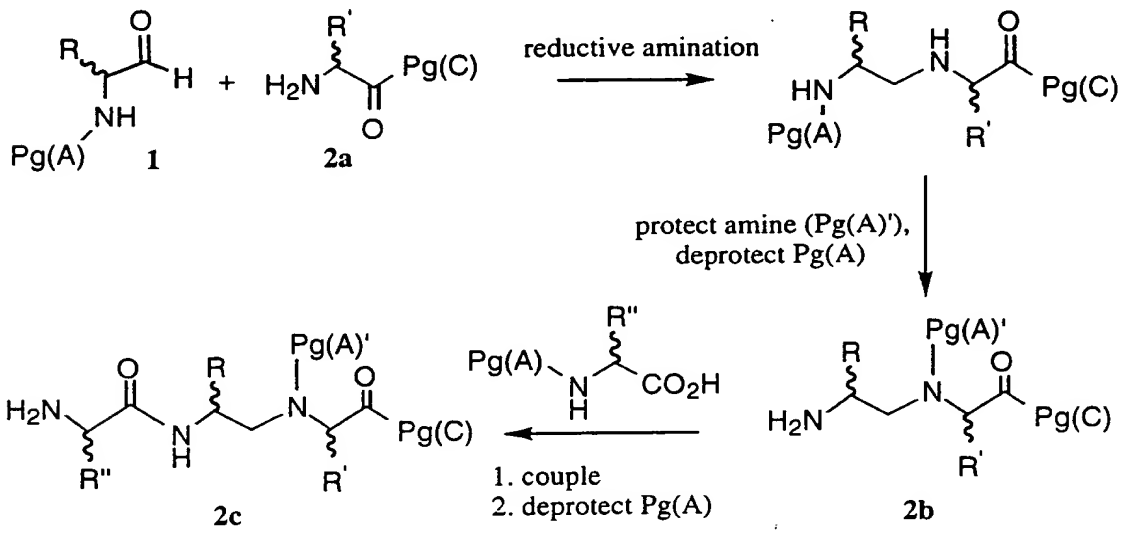


VI(i)a

The synthesis of all the mimetics described in this specification proceeds initially by the same general synthetic procedure for formation of the common intermediates - reaction of imines **3** with allyl metal reagents **Rg1** (allyl boranes preferred) or enolates **Rg2** (boron enolates preferred) to give **4** or **5**, as described in Scheme 1. These reactions, which also fall within the scope of the invention, involve the same general mechanism and are remarkable for their mildness and selectivity - allowing a wide range of functional groups to be present in the rest of the molecule, a very important consideration in the synthesis of peptide mimetics. Scheme 1 and all subsequent Schemes describe the preferred case of R^N=NHPg(A) and R^C=C(O)Pg(C) (Figures 1 and 2), analogous methods apply in the general case.

In relation to Scheme 1, preparation of the imines **3** is completed by condensation of an amino acid aldehyde (compound **1**) with an amine (**2a-d**). The aldehydes **1** may be prepared by either oxidative procedures from the corresponding N-protected amino alcohol, or reduction of an N-protected amino acid derivative[Fehrentz, 1983 #14], the

different approaches have been reviewed,[Jurczak, 1989 #22] (see also Goel et al., *Org. Syn.* **67**:69, 1988). The amines **2a** are amino acid esters (or other acid protected amino acid derivatives), which are commercially available or may be synthesised by standard procedures from amino acids. Amines **2b-2d** are prepared by reductive amination of an amine **2a** and an amino acid aldehyde **1**:



Amines **2d** are prepared by repeated coupling/deprotection steps (as in conversion of **2b** to **2c**), standard techniques of peptide synthesis.

The reductive amination procedure for the alkylation of amines by aldehydes is well established in the art.(See for example Sasaki and Coy, Peptides, 8:119, 1987), the preferred reagents are sodium cyanoborohydride,[Borch, 1971 #338; Hutchins, 1979 #366; Gribble, 1985 #367] or more preferred sodium triacetoxyborohydride.[Abdel-Magid, 1996 #337]

Methods for the formation of amide bonds (coupling) are well established in the art. For coupling at more hindered amines the use of certain reagents, for example those based on 1-hydroxy-7-azabenzotriazole,[Ehrlich, 1993 #320; Carpino, 1994 #368] or the use of amino acid fluorides[Wenschuh, 1994 #370; Carpino, 1990 #369] is advantageous.

Protecting strategies for the synthesis of peptides and peptide mimetics are well established in the art, for example a five dimensional orthogonal strategy was used by Hirschmann and co-workers in the synthesis of a somatostatin mimetic.[Hirschmann, 1996 #262] A more general reference work on protection/deprotection is the monograph by Greene and Wuts.[Protecting Groups]

The example syntheses described in this document use solution phase chemistry. The mimetics may also be synthesised by analogous solid phase techniques, or by a combination of solid phase and solution phase techniques, or the mimetics may be incorporated in normal solid phase peptide synthesis as with normal protected amino acids. A recent review by Früchtel and Jung[Früchtel, 1996 #371] details the state of the art in solid phase organic synthesis.

It will be clear to those skilled in the art that the mimetics of the invention, due to their generic methods of synthesis, are suited to the application combinatorial chemistry techniques (more specifically combinatorial organic synthesis) and certain associated identification and screening techniques. The application of combinatorial and associated technologies to drug discovery are well known in the art have been reviewed, see for example papers by Gallop et al. and by Gordon et al., and references therein, incorporated herein by reference [Gallop, 1994 #403; Gordon, 1994 #402].

The imines **3** form rapidly at room temperature on mixing of the amine and aldehyde in an appropriate solvent, e.g. CH_2Cl_2 or diethyl ether, with liberation of water. The water is removed with a drying agent, e.g. dried $MgSO_4$, which is removed by filtration. The imines are then reacted with an allyl metal reagent (**Rg1**) or an enolate (**Rg2**) to give, after work-up, compounds **4** or **5**.

In relation to reagents **Rg1** and **Rg2**, standard allyl organometals, such as allyl magnesium bromide, are unsuitable for reaction with imines **3** due to a lack of selectivity for the imine function over the carboxylic acid derived groups (esters, amides) also present in **3**. Allyl copper and zinc reagents have been used in selective reactions with imines,[Basile, 1994 #298; Bocoum, 1991 #294] but in the case of imines **3** these reagents result in extensive racemisation at the α-imine chiral centre, and attack esters

present in the imine to a significant extent. While some of the desired target **4** is produced by most allyl metal reagents on reaction with **3**, the reaction product typically contains a mixture of four diastereomers and also by-products from reaction at the carboxylic acid derived groups. In contrast to these results, reaction of the imines **3** with allyl boranes, such as B-allyl-9-borabicyclo[3.3.1]nonane (allyl-9-BBN) (**Rg1a**) gives excellent results. The use of allyl trialkylboranes with appropriate chiral alkyl groups such as B-allyl-diisopinocampheylborane (allyl-DIP, **Rg1b** and **Rg1c**), or the diisocaranylboranes **Rg1d-e** gives only a single product (one diastereomer, >99:1) in good yield and purity. The use of crotyl (**Rg1f**, **Rg1h-i**), methallyl (**Rg1g**) or other substituted allyl derivatives leads to bridge substituted mimetics (mimetics where at least one of M, M' and M" is not hydrogen). The less reactive allyl boronate allyldimethoxyboron (**Rg1j**) was found to give inferior results (significant epimerisation at Cα(i)) compared to the allyltrialkylboranes. Many allylboronate and related reagents (e.g. **Rg1k-m**) are described in the literature, and some of these may be more effective for the conversion of **3** to **4**. Selective reactions using allylic metals have been reviewed by Yamamoto and Asao, tables IV and V in the review (pp.2224-2230) list a wide variety of allyl boron reagents.[Yamamoto, 1993 #264] The preparation of allyl-9-BBN and other allyltrialkylboranes has been described by Brown and coworkers.[Kramer, 1977 #285; Brown, 1986 #363; Brown, 1984 #302; Brown, 1983 #303; Brown, 1990 #301] Allyltrialkylboranes may also be prepared by the reaction of the corresponding B-chloro or B-methoxy derivative with an allylmagnesium bromide (-78°C, diethyl ether), and reacted in situ with the imine.[Yamamoto, 1993 #264]

The reaction of ester enolates (**Rg2**, Figure 4) with imines has been quite thoroughly investigated as an important route to β-lactams.[Corey, 1991 #365; Hart, 1989 #364] Only enolates suitable for reaction with enolizable imines containing carboxylic acid derivatives (i.e. **3**) are useful for the conversion of **3** to **5**. Preferred reagents are (vinyloxy)boranes (boron enolates) and (vinyloxy)stannanes (tin enolates), Figure 4 illustrates some of these reagents by way of example, not limitation.

In relation to protection and deprotection of compounds **4** and **5**: addition of formaldehyde solution to **4** or **5** results in the formation of imidazolidines **6** or **7**. This protection strategy is important for further reaction of these compounds. The protecting group is removed by treatment with aqueous acid. A similar protection system is the dibenzyltriazone group of Knapp and co-workers,[Knapp, 1992 #88] the paper describes deprotection conditions and is incorporated herein by reference. An alternative deprotection method involves the hydrogenation of the imidazolidine system to an amine N-methyl group (40psi H_2, Pd-C, MeOH, 48hrs), a conversion that can be used to give mimetics where Z=Me.

In relation to deprotection of **5** to give acids **7**: deprotection methods for the ester or thioester -XR vary depending on the nature of the protecting groups being used. For general protecting group strategies refer to the references previously cited, e.g. Greene, protecting groups.

In relation to oxidation of alkenes **6**: aldehydes/ketones **9** may be synthesised directly from **6** by ozonolysis (for methods see for example the monograph by Hudlicky[Hudlicky, #373]), or in a two step process of dihydroxylation (OsO_4, N-methylmorpholine-N-oxide (NMO), t-BuOH/water)[VanRheenen, 1976 #372; Ray, 1980 #313] to **8** followed by oxidative cleavage ($Pb(OAc)_4$, benzene)[Hudlicky, 1990 #373].

In relation to reduction of acids **7** to aldehydes **9**: carboxylic acids **7** can be converted to aldehydes by the same general methods used for the formation of protected α-amino aldehydes described above.[Jurczak, 1989 #22] The carboxylic acid can be selectively reduced to the alcohol in the presence of carboxylic esters by the use of borane,[Brown, 1979 #376] then oxidised to the aldehyde as previously described.[Jurczak, 1989 #22] An alternative route to the aldehydes **9** is the direct reduction of **5**. For example thioesters (**5**, XR=SEt) may be reduced to aldehydes by the method of Fukuyama, using Et_3SiH and Pd-C.[Fukuyama, 1990 #375]

In relation to **Scheme 2**: Aldehydes/ketones **9** undergo reductive amination with amino esters **10** by the methods previously described. The preferred method is $NaBH(OAc)_3$ in dichloroethane (room temperature).

In relation to **Scheme 3**: Deprotection of **11** is by standard methods consistant with the overall protecting strategy, as previously discussed. Many coupling agents are suitable for effecting the cyclisation of **12** to **13**, typical conditions: THF, BOP or HBTU or HATU, $EtN(i\text{-}Pr)_2$. The imidazolidine group is then deprotected (as previously described) by hydrogenation (MeOH, H_2-Pd/C) when Z=Me, and by hydrolysis (H^+, H_2O) for Z=H (other Z groups may be introduced by acylation or alkylation of the deprotected secondary amine).

In relation to **Scheme 4**: Deprotection and cyclisation of **5b** to **I(ii)** - where X=S (thioester) cyclisation of **14** may occur without the need for deprotection/coupling. Otherwise standard deprotection and coupling (cyclisation) methods are used. Other conversions are as previously described.

In relation to **Scheme 5**: As previously discussed, coupling reactions to relatively hindered (usually secondary) amines often require the use of specialised coupling conditions such as acid fluorides **17**, as described by Carpino et al.[Wenschuh, 1994 #370; Carpino, 1990 #369] Protecting groups Pg(A)' and Pg(C)' (in **18**) are typically benzyloxycarbonyl (Cbz) and benzyl ester, simultaneously deprotected by hydrogenation (0.1M HCl in EtOH, H_2-Pd/C), cyclised using the BOP coupling reagent in THF or DMF, followed by conversion (deprotection) of the imidazolidine group to N-Me by hydrogenation as previously described.

In relation to **Scheme 6**: Standard deprotection/ coupling conditions as previously described.

In relation to **Scheme 7**: Where R^4 is a β-branched amino acid side chain (such as in Valine) then the coupling of **7a** and **22** may require the use of HATU or other system suitable for a hindered coupling. Conditions and protecting groups for the conversion of **23** to **21** are the same as for the conversion of **18** to **II(i)**, Scheme 5.

In relation to **Scheme 8**: Hydroboration of alkenes is well known in the art, see for example monographs by Brown.[Brown, 1975 #378; Pelter, 1988 #377] The resulting alkyl boranes can be oxidised to alcohols (using alkaline hydrogen peroxide, or in a preferred embodiment using trimethylamine oxide, or other amine oxide, to form the

borate with subsequent liberation of the alcohol by transesterification).[Soderquist, 1986 #379] Alternatively, treatment of the borane with acid dichromate or, in a preferred embodiment, with pyridinium chlorochromate (PCC) gives the aldehyde.[Brown, 1980 #381; Brown, 1986 #380] The aldehydes so formed may be reductively aminated on to amines **10** by the methods previously described.

In relation to **Schemes 9-11**: Standard synthetic techniques, previously described.

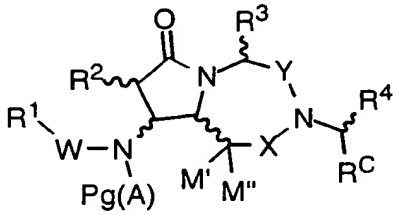
Methods for the synthesis of beta bulge (n=1, **III(i-iv)**) and higher loop mimetics (n>1), follow the corresponding methods for the synthesis of beta turn mimetics **II(i-iv)**. Appropriate protecting groups are chosen so that extra residues can be added to the system prior to cyclisation, as illustrated in Scheme 11 for the synthesis of a **III(i)** mimetic.

In relation to **Scheme 12**: Conversion of 1,2-diols **8** to epoxides **31** (dehydration) may be achieved with a number of reagents, for example triphenylphosphine and a dialkylazodicarboxylate (the Mitsunobu reagents)[Carlock, 1978 #327; Robinson, 1983 #326] or TsCl/NaOH/$PhCH_2NEt_3^+$ Cl^-.[Szeja, 1985 #382] The epoxides **31** alkylate amines **10** on warming in ethanol solution to give the amino alcohols **32**. The alcohol may then be oxidised to the ketone **34** by the use of TPAP (tetrapropylammonium perruthenate) with N-methylmorpholine-N-oxide in CH_2Cl_2/acetonitrile by the method of Griffith and Ley.[Griffith, 1990 #383] For **34** typically Pg(A)'=Cbz and Pg(C)'=O-benzyl, then by the use of catalytic hydrogenation conditions (EtOH, H_2-Pd/C) the protecting groups are both removed and intramolecular reductive amination of the free amine to the ketone occurs to give **35**. Coupling using the BOP reagent (or other suitable conditions) followed by deprotection of the imidazolidine group as previously described gives the bicyclic mimetic **IV(i)**. Alternative syntheses are possible with the use of mild oxidising reagents to convert the glycols to carbonyl compounds, followed by reductive amination [Frigerio, 1994 #401].

In relation to **Scheme 13**: 1,2 diols can be oxidised without carbon-carbon bond cleavage by the use of certain mild reagents e.g. IBX [Frigerio, 1994 #401]. Conversion

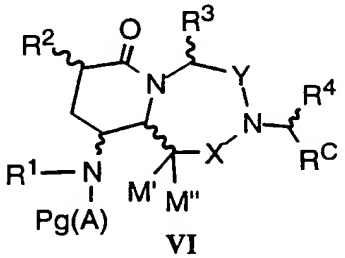
of **37c** to **38** proceeds by intramolecular reductive amination, or alternatively **37a** can be reductively aminated onto **2b**, as indicated. Reductive amination, coupling and deprotection details are as previously described.

The syntheses for the neutral bicyclic β-turn mimetic systems **V** and **VI** are accomplished from the corresponding γ-turn mimetic systems **I**, where the R^1 side chain group is derived from an aspartic acid (**V**) or glutamic acid (**VI**) derivative. .



V

	X	Y
V(i)	CH(M)	C(O)
V(ii)	C(O)	CH_2



VI

	X	Y
VI(i)	CH(M)	C(O)
VI(ii)	C(O)	CH_2

The synthesis of mimetics **V** and **VI** thus proceeds as in Scheme 1, with the aldehyde component **1** (Scheme 1) being of the form **1d** or **1e** (Scheme 14), with the R and Pg groups as previously defined. The synthesis follows the synthesis of γ-turn mimetic systems **I**, and is completed by the method illustrated in Scheme 15.

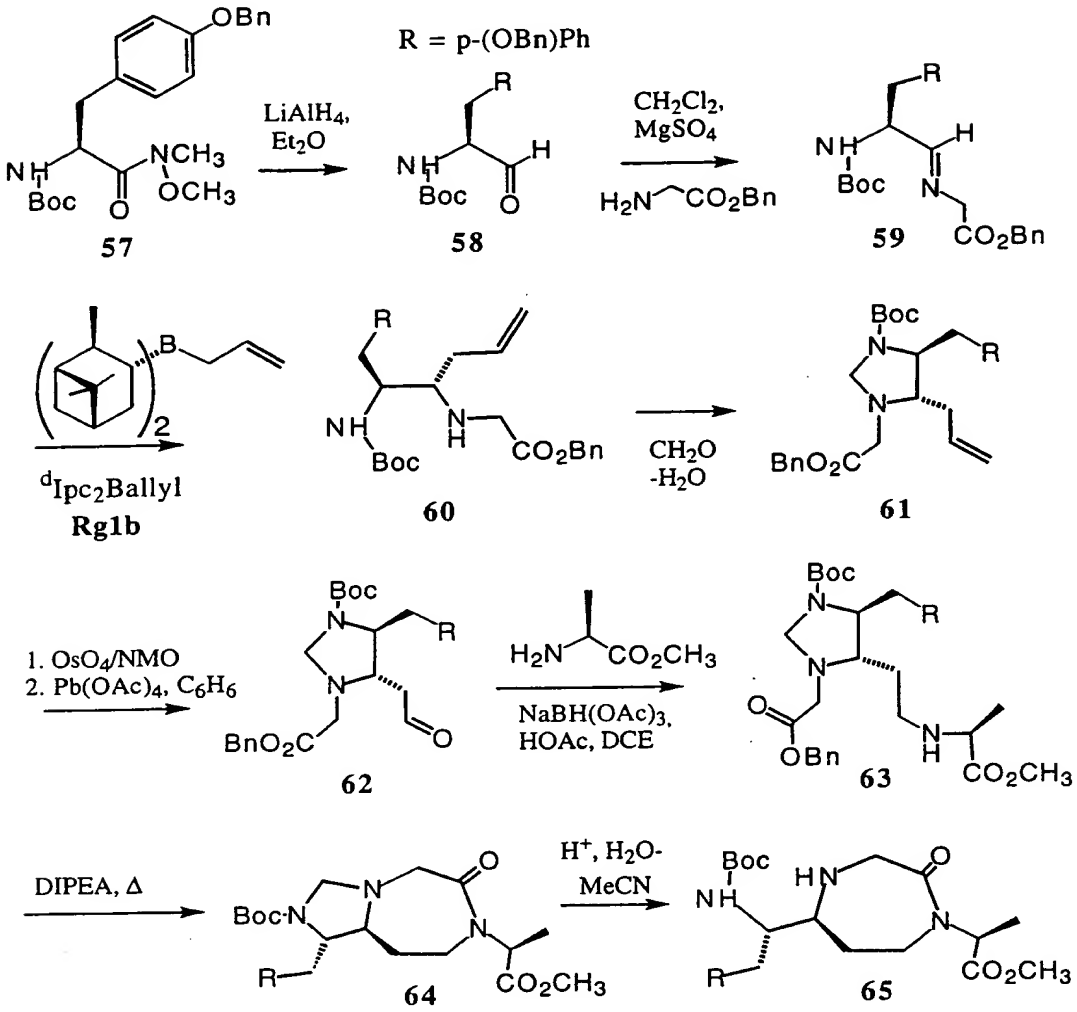
In relation to the preparation of alkylated aspartic and glutamic acid derivatives **1d** and **1e** the alkylated derivatives **41-44** can be prepared by a number of methods known in the art. Selected methods are summarised in Schemes 16 and 17. Rapoport and co-workers have developed methods for the selective alkylation of N-phenylfluorenyl protected aspartic and glutamic acid derivatives.[Koskinen, 1989 #385; Wolf, 1989 #384] A review by Sardina and Rapoport describes several methods for the synthesis of alkylated aspartic and glutamic acid derivatives, incorporated herein by reference.[Sardina, 1996 #386] Derivatives **41-44** are converted to aldehydes **1d** and **1e** by the methods previously described for for the preparation of aldehydes **1**. The use of standard chemical techniques to modify the aspartic and glutamic acid derivatives, or the use of similar derivatives of non-natural amino acids, such as homo-glutamic acid,

enables the synthesis of the other compounds of the invention in which Q^1-Q^2 (in the general structure **X**) forms part of a cyclic system.

An alternative simplified synthetic procedure for intermediate compounds **11** (or equivalent) is possible in the case where R^1 is hydrogen and M, M' and M" are also hydrogen, as described in Scheme 18. Compound **51** is available commercially with certain N-protecting groups or can be made by coupling N-protected glycine with N,O-dimethylhydroxylamine. Reaction with vinylmagnesium bromide according to the general procedure of Rapoport and co-workers[Cupps, 1985 #10; Boutin, 1986 #5] results in formation of the α,β-unsaturated ketone **52**. Conjugate addition of an amino acid ester (**10**) (0°C, THF) results in the formation of aminoketones **53** which are N-protected by standard procedures before reductive amination of an amino acid ester under the conditions described by Abdel-Magid et al.[Abdel-Magid, 1996 #337] ($NaBH(OAc)_3$, dichloroethane) to form **55**. Deprotection and reaction with formalin in THF gives **11**, or deprotection and coupling gives the γ-turn mimetic **I(i)a**, as indicated.

EXAMPLE SYNTHESES

(A) Synthesis of a γ-turn mimetic **I(i)** by the general procedure



The amide **57** was synthesised from commercially avaliable Boc-Tyrosine(OBn)OH by coupling with N,O-dimethylhydroxylamine (BOP, CH_2Cl_2, DIPEA). To a stirred solution of 4.2g of amide **57** in 100mls of anhydrous diethylether cooled to 0°C was added 0.51g lithium aluminium hydride. After 10 minutes a solution of 1.5g $NaHSO_4$ in 30mls of water was added. The reaction mixture was diluted with more ether and washed with 1M HCl, saturated aqueous sodium bicarbonate and brine and dried over magnesium sulphate. The volatiles were removed under reduced pressure to give a waxy solid which was precipitated from cold ether/hexane to give 2.6g (72%) of crude **58**. A 0.5molar

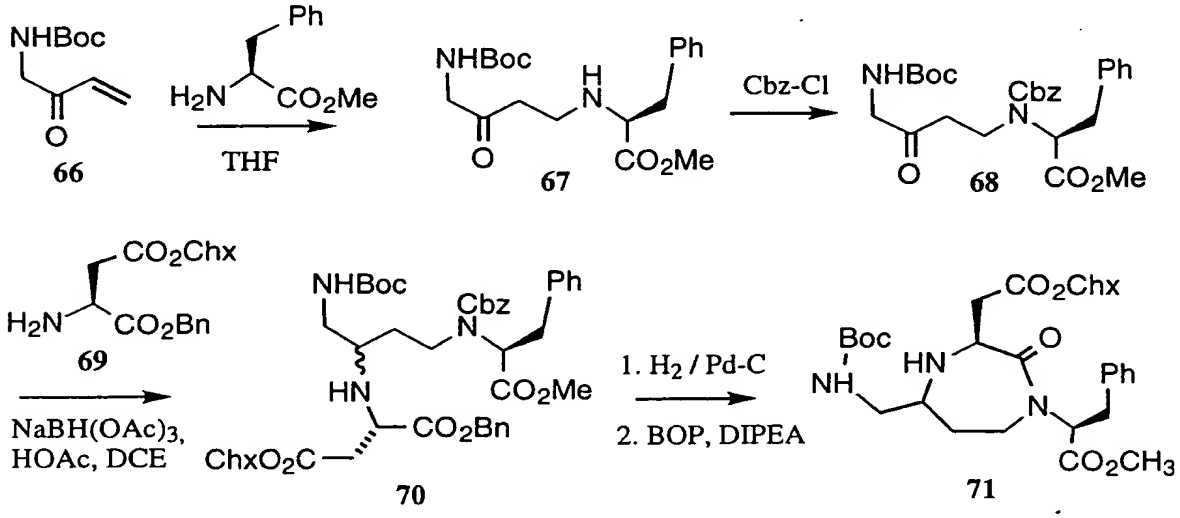
solution of $^{d}Ipc_2Ballyl$ was prepared by the addition of allylmagnesium bromide to one equivalent of (+)DIP-Cl in anhydrous diethyl ether under dry nitrogen. The imine **59** was formed by the reaction of the aldehyde (1.4g) with one equivalent of glycine benzyl ester in CH_2Cl_2, the water formed was removed with magnesium sulphate which was then removed by filtration. The imine solution was stirred and cooled to -78°C under dry nitrogen and one equivalent of the previously prepared $^{d}Ipc_2Ballyl$ solution added. The mixture was allowed to warm gradually to room temperature (overnight). The volatiles were removed under reduced pressure and the residue dissolved in THF and 1ml of glacial acetic acid added. The mixture was refluxed overnight and then the volatiles removed under reduced pressure. The crude product was dissolved in CH_2Cl_2 / petroleum ether and the precipitate filtered off. The residual oil was chromatographed on flash silica eluting with ethyl acetate / petroleum ether to give 1.3g (60% yield based on **58**) of **60**. To a stirred ethyl acetate solution of **60** was added a few drops of formalin (40% aqueous formaldehyde), **61** was rapidly formed. The ethyl acetate solution was washed several times with water then with brine and then dried over magnesium sulfate. To 220mg of **61** 60mg of N-methylmorpholine-N-oxide (NMO), 40mg of a 2.5% (by weight) solution of osmium tetroxide in t-butanol, 4mls of t-butanol and 0.5mls water. The mixture was stirred at room temperature until the reaction was complete (about 24 hours). 3mls of 10% $NaHSO_3$ was added, the solution stirred for 10 minutes, then neutralised with sodium bicarbonate, diluted with brine and extracted several times with ethyl acetate. The combined extracts were washed with brine and dried over magnesium sulfate. Removal of volatiles under reduced pressure gave the crude diol as an oil which could be purified by chromatography on silica gel. To a stirred solution of 100mg of the diol in 4mls of dry benzene over 4Å molecular sieves was added 85mg of acetic acid moistened $Pb(OAc)_4$. The product was directly purified on silica gel eluting with 25% ethyl acetate in light petroleum ether (32% yield). The aldehyde was reductively aminated on to glycine methyl ester with $NaBH(OAc)_3$ / dichloroethane to **63**, some of which cyclised under the reaction conditions to **64**. The cyclisation was completed by addition

of base (DIPEA) and warming of the solution, and the imidazolidine ring deprotected with a dilute solution of trifluoroacetic acid (0.1%) in acetonitrile-water to give **65**.

(B) Synthesis of a γ-turn mimetic **I(i)** by the short procedure (for R^1 = hydrogen)

To a solution of 11.6g of **51** (Pg(A)=Boc) in 100mls dry THF, magnetically stirred under dry nitrogen and cooled to 0°C, was added 120mls of freshly prepared vinly magnesium bromide (about 1M in THF). The mixture was stirred for 2 hours and then poured into a 1:1 mixture of crushed ice and 1M HCl. The resulting solution was extracted twice with CH_2Cl_2, the combined extracts were washed with water then brine then dried over magnesium sulfate (removed by filtration) and the volatiles removed under reduced pressure. The crude product contained about 9g of **66** (90% yield). To 3g of crude **66** dissolved in THF (50ml) was added 4g of phenylalanine methyl ester hydrochloride and about 10 mole% DIPEA. The mixture was stirred for 2 hours then diluted with about 400mls cold 1M HCl and extracted twice with CH_2Cl_2, the aqueous solution was neutralised with sodium bicarbonate and extracted with diethyl ether. The ether solution was washed with water twice then brine and then dried over magnesium sulfate (removed by filtration) and the volatiles removed under reduced pressure to leave 6.1g of crude **67**. The crude aminoketone (4g) was dissolved in ethyl acetate (50mls) and a solution of 3g potassium bicarbonate in 10mls water added. To the vigorously stirred mixture cooled to 0°C was added 1.7mls of 95% benzy chloromormate (dropwise). The stirred reaction mixture was allowed to warm to room temperature over 2 hours, then diluted with additional ethyl acetate and the organic layer separated and washed with 1M HCl, aqueous sodium bicarbonate then brine and then dried over magnesium sulfate (removed by filtration) and the volatiles removed under reduced pressure to leave the crude product as an oil which was purified by flash chromatography eluting with ethyl acetate-petroleum ether to give 3.8g of **68** (71% yield over 3 steps). To 1g of the ketone **68** dissloved in 10mls of dichloroethane was added the amine **69** derived from deprotection (TFA, CH_2Cl_2) of 1.3g of BocAsp(OChx)OBn and 0.87g of

sodium triacetoxyborohydride. The reaction was stirred for 48 hours at room temperature and then the volatiles removed under reduced pressure and the residue dissolved in diethyl ether and washed with 1M HCl (three times), aqueous sodium bicarbonate then brine and then dried over magnesium sulfate (removed by filtration) and the volatiles removed under reduced pressure to leave the crude product as an oil (1.6g). The crude reductive amination product (0.8g) was dissolved in about 30mls of 0.1M methanolic HCl and 110mgs 10%Pd on carbon added. Hydrogenation over 12 hours removed the benzyl ester and Cbz group. The methanol was removed under reduced pressure. 90% of the crude product was dissolved in 50mls THF and cyclised by the addition of 0.6g BOP reagent and 0.5g DIPEA. The mixture was stirred for 10 minutes at room temperature then diluted with ethyl acetate and washed with 1M HCl (twice), aqueous sodium bicarbonate then brine and then dried over magnesium sulfate (removed by filtration) and the volatiles removed under reduced pressure to leave the crude product which was chromatographed on silica eluting with about 2% ethanol in chloroform to yield 320mg (65% from the ketone **68**) of protected γ-turn mimetic **71**.

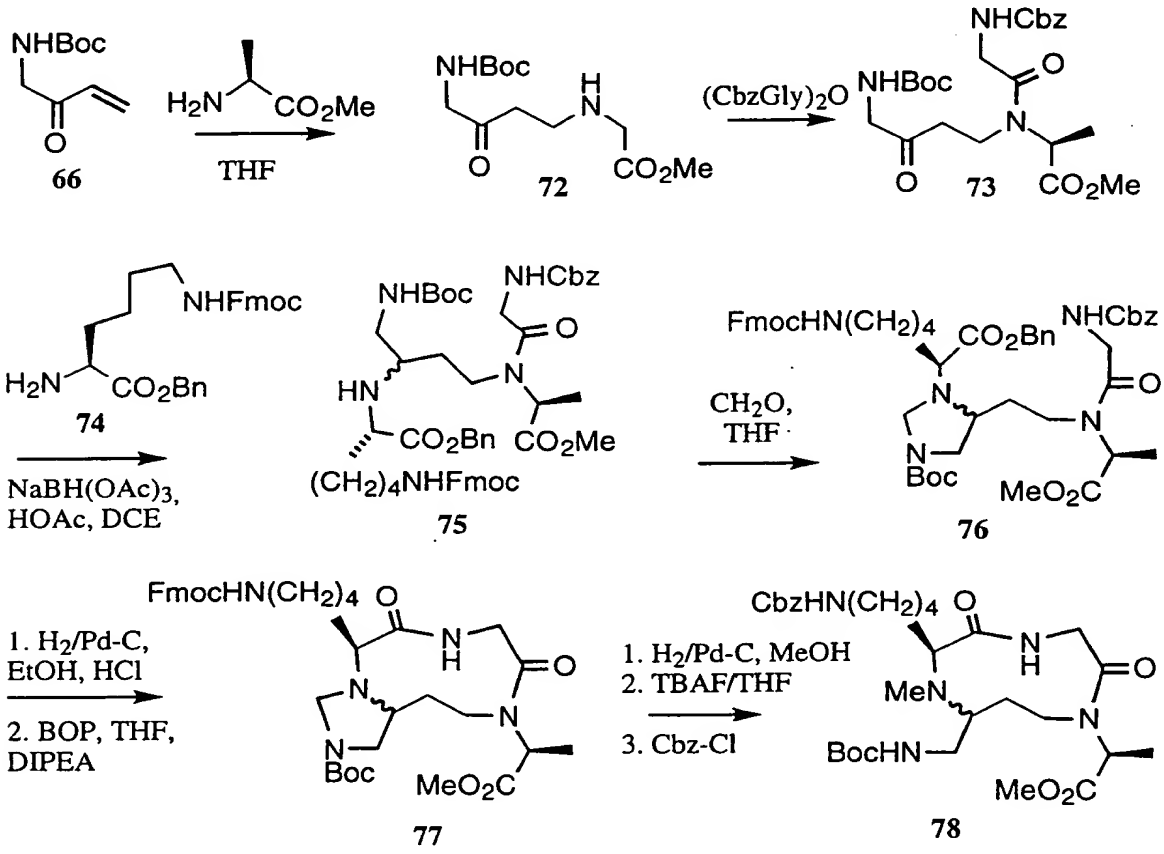


(C) Synthesis of a β-turn mimetic **II(i)**

Compound **66** was prepared as described above, and reacted with alanine methyl ester to form **72** using the same method as described for the synthesis of **67**. The crude amino

ketone **72** (1.22g) was reacted with Cbz-glycine symmetric anhydride (synthesised from 1.95g CbzGlyOH and 9.3mls 0.5M dicyclohexylcarbodiimide in dichloromethane) and 0.6g DIPEA in dichloromethane. The reaction was stirred at room temperature for 10 hours then diluted with ether (any DCU precipitate was filtered off) and the ether solution was washed with 1M HCl, aqueous sodium bicarbonate then brine and then dried over magnesium sulfate (removed by filtration) and the volatiles removed under reduced pressure to leave the crude product as an oil which was purified by flash chromatography eluting with 2:1 ethyl acetate:light petroleum ether, yield of **73** was 1.8g (90%). Reductive amination of **73** with **74** derived from the deprotection of BocLys(Fmoc)OBn (TFA, CH_2Cl_2) is carried out by the previously described method for the formation of **70** (71% yield after flash chromatography eluting with 2:1 to 3:1 ethyl acetate:light petroleum). The product amine **75** was dissolved in ethyl acetate and formalin added to the stirred solution resulting in the formation of imidazolidine **76**. The ethyl acetate solution was washed with aqueous sodium bicarbonate, water (twice), brine and then dried over magnesium sulfate (removed by filtration) and the volatiles removed under reduced pressure to leave the crude product as an oil which was purified by flash chromatography eluting with 3:2 ethyl acetate:light petroleum ether (yield >75%). The protected pre-cyclisation compound **76** (400mgs) was dissolved in 0.1M ethanolic HCl (20mls) and hydrogenated with 250mgs of 10% Pd-C. The hydrogenation was complete after 7 hours (about 40 psi H_2, room temperature). The solution was filtered through a celite pad to remove the catalyst and 50mls of DMF added. Volatiles (ethanol) were removed under reduced pressure then a solution of BOP reagent (300mgs) and DIPEA (300mgs) in 150mls of DMF was added and the mixture stirred at room temperature for 15 minutes. Most of the DMF was removed under reduced pressure and the residue dissolved in ethyl acetate and washed with 1M HCl, aqueous sodium bicarbonate, water (twice), brine and then dried over magnesium sulfate (removed by filtration) and the volatiles removed under reduced pressure to leave about 300mgs of crude product **77**. The crude product was dissolved in 30mls methanolic HCl (0.1M) and hydrogenated (200mgs Pd-C, 40psi H_2) for 24 hours reducing the imidazolidine to an N-methyl group.

The catalyst was filtered off (celite) and the solvent removed under reduced pressure, the residue was then treated with tetrabutylammonium fluoride in THF to remove the FMOC group. The free amine was then reprotected by addition of benzyl chloroformate (65mgs) and DIPEA (100mgs). After stirring for 1 hour ethyl acetate was added and the organic layer was washed with 1M HCl, water, then brine, dried over magnesium sulfate (removed by filtration) and the volatiles removed under reduced pressure to leave an oil which was purified by flash chromatography eluting with 3-5% ethanol in chloroform for a yield of about 40% of **78** based on **76**.

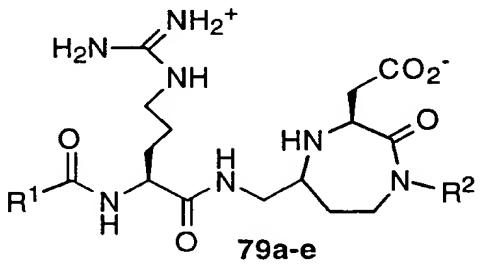


EXAMPLE OF THE UTILITY OF THE INVENTION

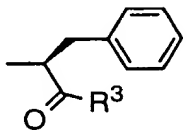
The peptide sequence arginine-glycine-aspartic acid (RGD) is important to the binding of proteins to certain integrin receptors, such as the $GP_{IIb\text{-}IIIa}$ receptor found on the surface of platelets. Several cyclic peptides having the RGD sequence have been found to antagonise the binding of plasma proteins to the $GP_{IIb\text{-}IIIa}$ receptor, thereby inhibiting blood clotting. $GP_{IIb\text{-}IIIa}$ antagonists have therapeutic potential as anti-thrombotics, there are several in early clinical trials[Humphries, 1994 #174]. Mimetics based on γ-turn structures centred on the Asp residue have been successful, this structure was chosen to test the compounds of the invention.

Five (Arg-Gly-Asp-Phe) mimetics containing the γ-turn system were synthesised (Figure 1). A preliminary functional assay for binding to the human platelet $GP_{IIb\text{-}IIIa}$ integrin was carried out. The assay used was inhibition of clotting in whole blood induced by ristocetin, as measured by light scattering. Inhibition was measured by comparison with the peptide $AcRGDSNH_2$. Tests were carried out on **79b**, **79d** and **79e**. The best inhibition was obtained for **79d**, with preliminary results indicating a low micromolar IC_{50}.

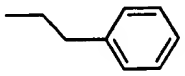
The γ-turn mimetic compounds synthesised are low in molecular weight (500-600amu) and their synthesis is short and high yielding, making them attractive leads for the development of an orally bioavailable drug.



79a-e

79a-c: $R^1 = CH_3$, $R^2 =$ 

79a $R^3 = OCH_3$
79b $R^3 = OH$
79c $R^3 = NH_2$

79d $R^1 = OtBu$ **79d&e**: $R^2 =$ 

79e $R^1 = CH_3$

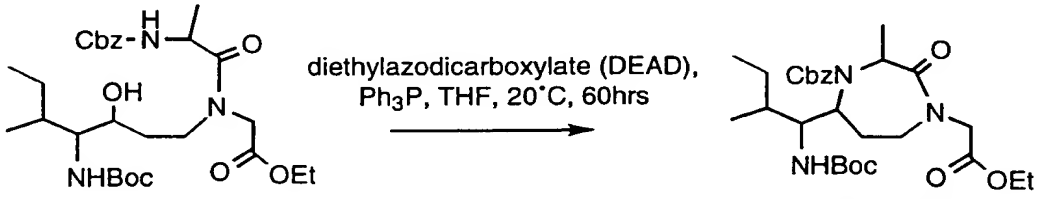
APPENDIX

Previous reports of the γ-turn mimetic system **I(i)**

A theoretical study of the suitability of various heterocyclic systems as a γ-turn mimetics has recently been published[Alkorta, 1996 #180]. The study included the 1,3,5-substituted-1,4-diaza-2-oxocycloheptane system (the basis of the γ-turn mimetics described herein). No synthesis was described or referenced in the paper for this mimetic system, in contrast to other known systems where the synthesis was referenced.

Although a search of the Chemical Abstracts registry file on the substructure of the γ-turn system gave only the above modelling study, we are aware of a reported synthesis of the γ-turn mimetic system by a different synthetic approach. The alternative approach was described in a poster presented at the 23rd European Peptide Symposium (1994), and repeated at the end of a review published in the Bulletin of the Chemical Society of Belgium [Guilbourdenche, 1994 #179]. Our research and other literature results do not support this alternative method. It is highly probable the report is in error and does not represent a reduction to practice. A summary of the main points leading to this conclusion is presented below.

The key step in the proposed synthesis is the cyclisation of (**i**) to the protected target (**ii**) using the Mitsunobu reagents:



(**i**) (**ii**), 40%

No spectroscopic data were presented for any of the compounds described in the proposed synthesis.

(1) Difficulty of forming seven membered rings via the Mitsunobu reaction

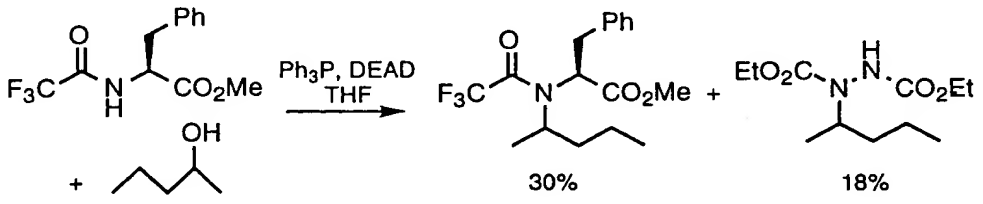
(a) Literature precedent

The literature on the formation of cyclic amines and amides with the Mitsunobu reaction contains numerous examples of the formation of 3-6 membered rings[Bernotas, 1991 #113; Henry, 1989 #93; Pfister, 1984 #112; Kelly, 1986 #114; Robinson, 1983 #326; Carlock, 1978 #327], but very few cases of seven membered ring formation. In one paper on the cyclisation of amino alcohols the faliure to form a simple seven membered target is specifically described.[Bernotas, 1991 #113] In the organic reactions entry on the Mitsunobu reaction[Hughes, 1992 #90] three instances of seven membered ring formation with carbon-nitrogen bond formation are described: all three involve a primary alcohol, two occur in polycyclic systems and appear to be special cases, and the third involves alkylation of a hydroxamide - far easier than an amide due to higher NH acidity.

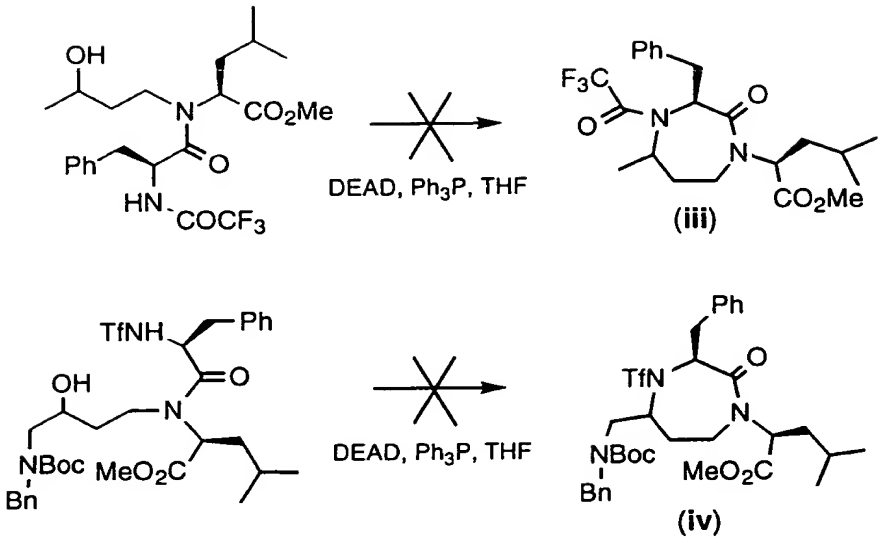
There appears to be no literature precedent for the formation of a seven membered ring to a simple amide or carbamate nitrogen. In addition there is little precedent for secondary amide N-alkylation with hindered secondary alcohols, as is proposed to occur in the formation of (**ii**).

(b) Synthetic studies

Extensive studies on the use of the Mitsunobu reaction for the formation of the target system were carried out in our laboratories prior to becoming aware of the proposed synthesis. In our hands this approach was completely ineffective. The key reactions are described in Schemes Ap1 and Ap2.



Scheme Ap1

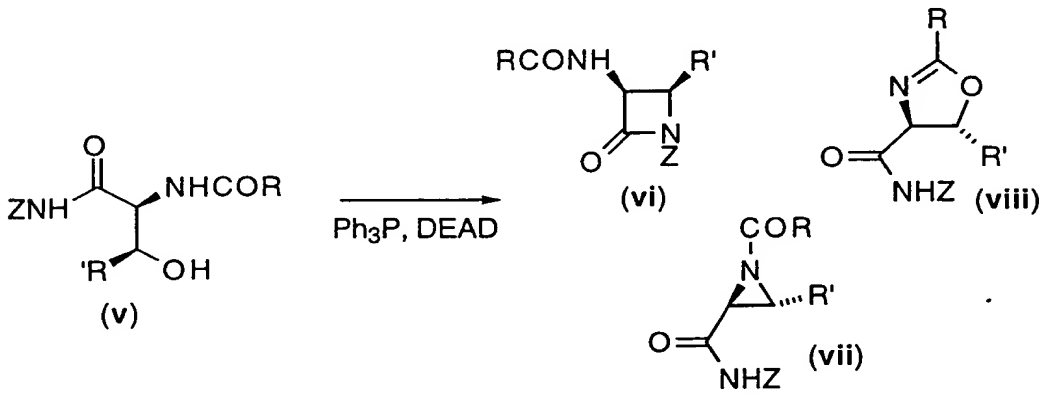


Scheme Ap2

The formation of the alkylation product was somewhat successful in the intermolecular reaction (Scheme Ap1), but this success was not repeated in cyclic systems (Scheme Ap2). No trace of the target cyclic products (**iii**) or (**iv**) was detected.

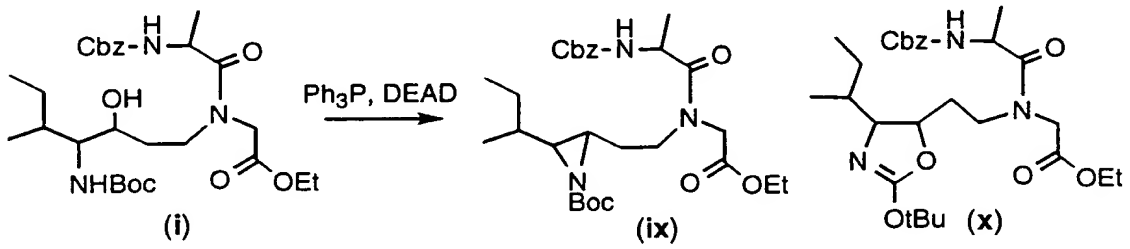
(2) Competing reactions

Cyclisation of β-hydroxy amide derivatives (**v**) with the aim of forming β-lactams (**vi**) also results in the formation of the aziridine (**vii**) and oxazoline (**viii**) products shown in Scheme Ap3.[Hughes, 1992 #90]



Scheme Ap3

As the Mitsunobu reaction is relatively effective for the formation of small ring sizes, it is quite probable that the formation of aziridines and oxazolines will compete with other possible cyclisations, other factors being equal. Such competition can take place in the proposed synthesis, the products would then be (**ix**) and/or (**x**), Scheme Ap4. Both the aziridine and oxazoline are isomeric with the target compound (**ii**), possibly leading to their confusion with the target, a situation easily resolved by ^1H NMR.



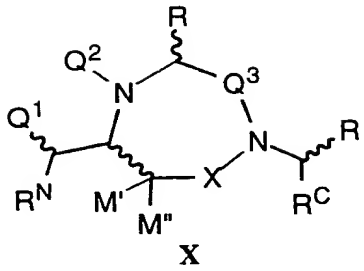
Scheme Ap4

In summary, it is highly probable that the proposed method is in error because:

- Literature contrindications, lack of precedent
- Extensive studies in our laboratories indicate the approach is ineffective
- Competing cyclisations produce isomeric products
- There are no spectral details in the publication
- The CA registry file has no entry for the system
- There have been no follow-up papers

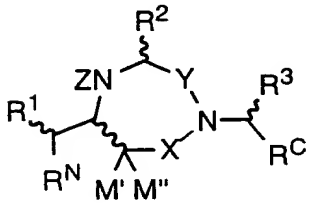
DATED this twenty-fourth day of March 1998.

THE UNIVRSITY OF QUEENSLAND,
By their Patent Attorneys,
FISHER ADAMS KELLY.



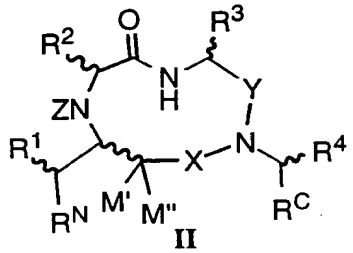
X

	X	Y
(i)	-CH(M)-	C(O)
(ii)	-C(O)-	CH_2
(iii)	-CH(Q^4)CH_2-	C(O)
(iv)	-CH(Q^4)C(O)-	CH_2



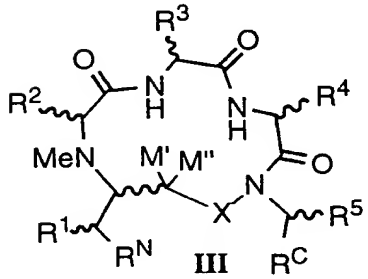
I

	X	Y
I(i)	CH(M)	C(O)
I(ii)	C(O)	CH_2



II

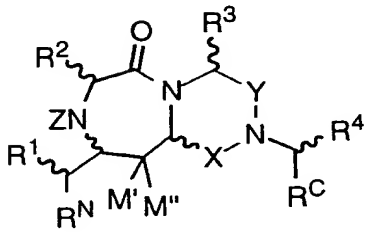
	X	Y
II(i)	CH(M)	C(O)
II(ii)	C(O)	CH_2
II(iii)	CH(M)CH_2	C(O)
II(iv)	CH(M)C(O)	CH_2



III

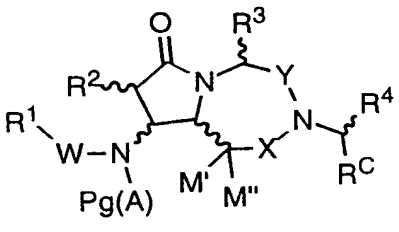
	X	Y
III(i)	CH(M)	C(O)
III(ii)	C(O)	CH_2
III(iii)	CH(M)CH_2	C(O)
III(iv)	CH(M)C(O)	CH_2

Figure 1. General structure of the mimetic systems and preferred cyclic turn and loop mimetic systems. Refer to the main text for a full description of the Q, R, Pg, Z and M groups.



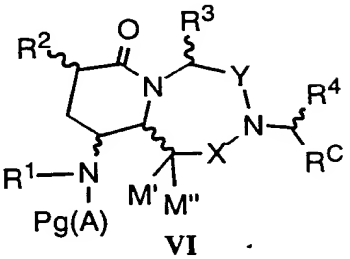
IV

	X	Y
IV(i)	CH_2	C(O)
IV(ii)	C(O)	CH_2



V

	X	Y
V(i)	CH(M)	C(O)
V(ii)	C(O)	CH_2



VI

	X	Y
VI(i)	CH(M)	C(O)
VI(ii)	C(O)	CH_2

Figure 2. Bicyclic beta turn mimetic systems. Refer to the main text for a full description of the R, Pg, Z and M groups.

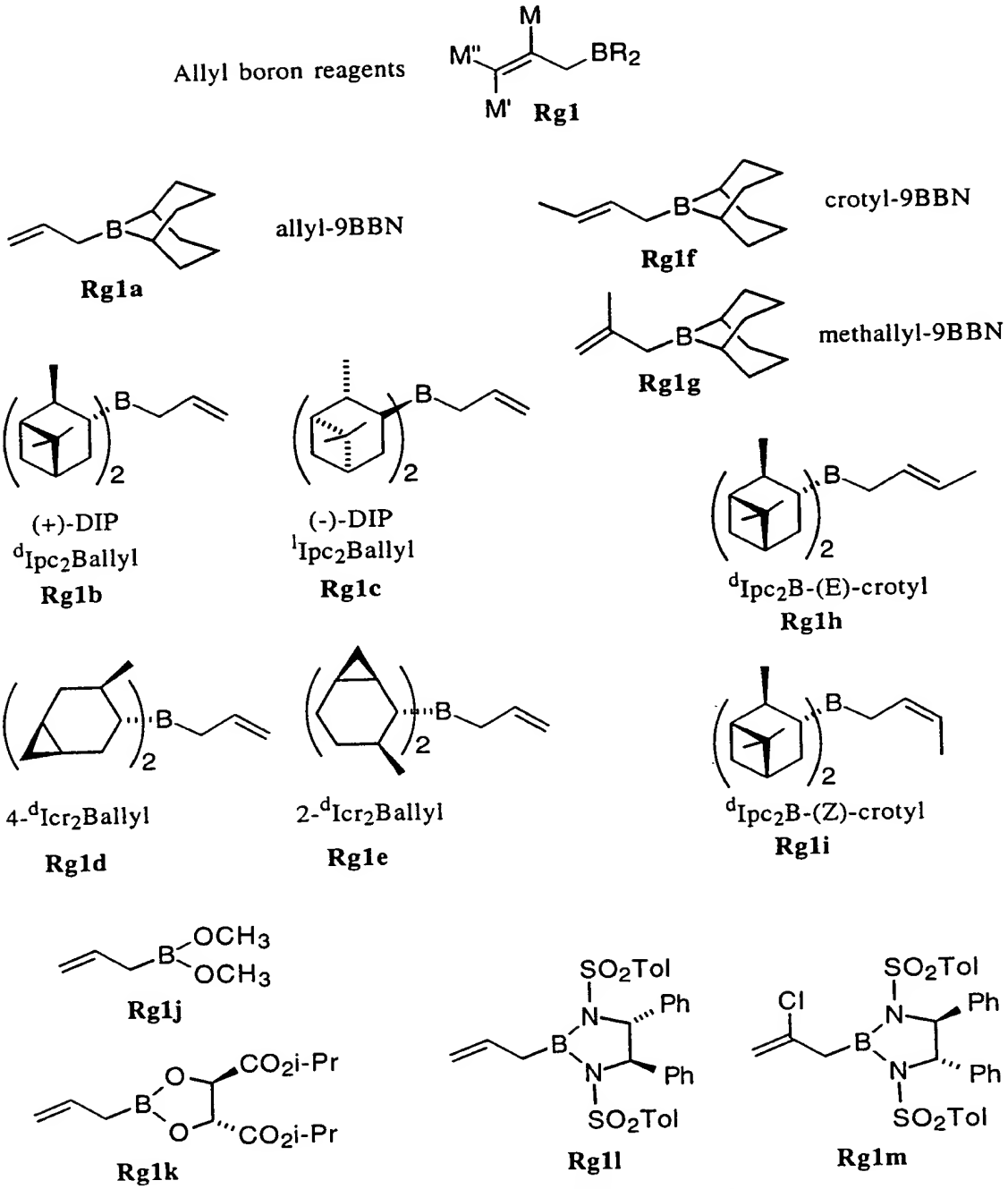


Figure 3. Selected allylboron reagents

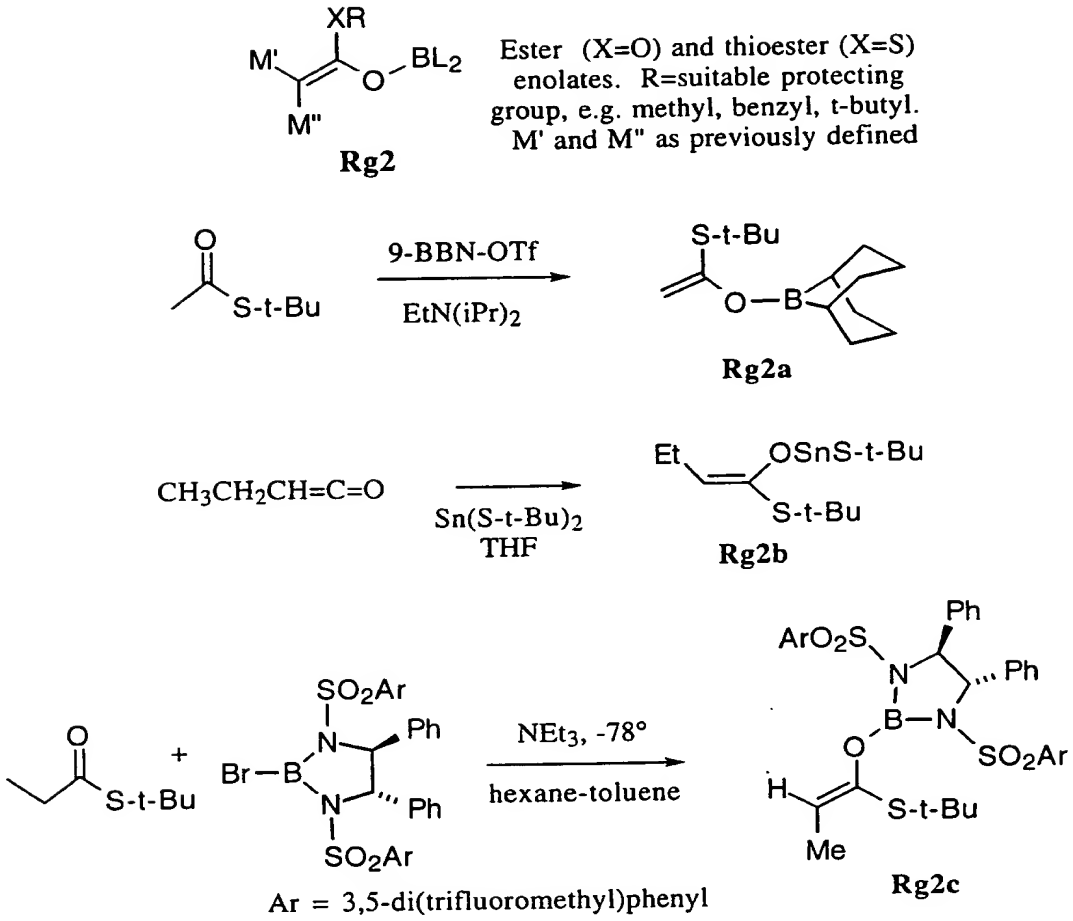
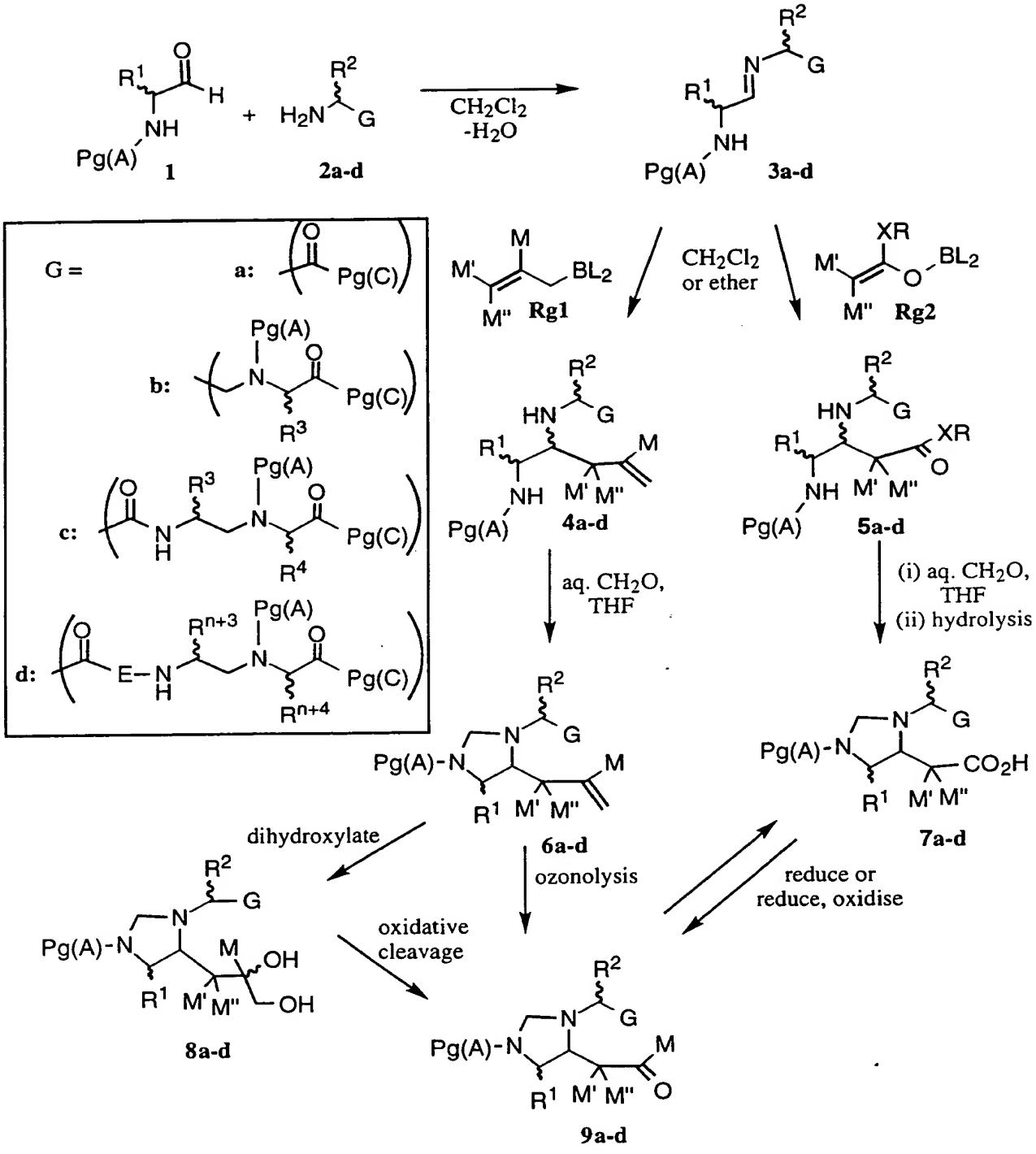
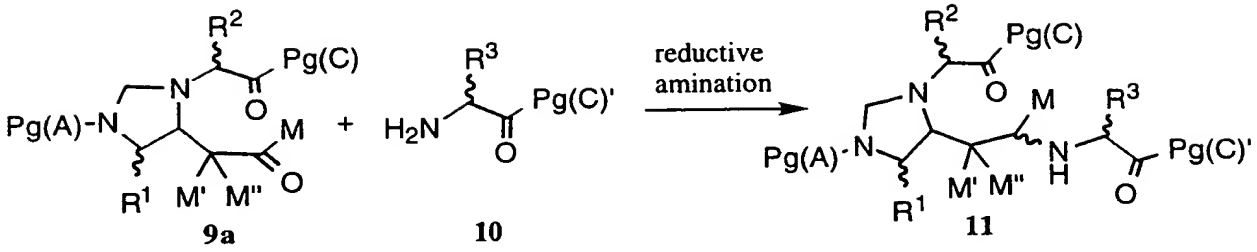


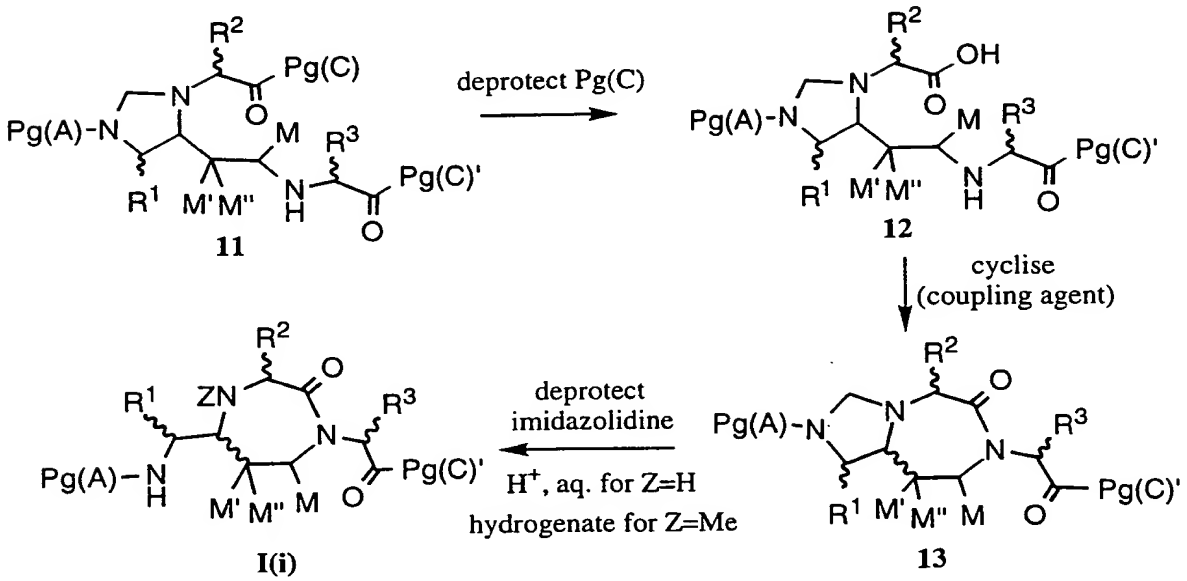
Figure 4. Selected enolates with some preparation details


1
2a-d
CH_2Cl_2
$-H_2O$
3a-d
G =
a:
b:
c:
d:
Pg(C)
Pg(A)
Rg1
Rg2
CH_2Cl_2
or ether
4a-d
5a-d
aq. CH_2O,
THF
(i) aq. CH_2O,
THF
(ii) hydrolysis
6a-d
7a-d
ozonolysis
dihydroxylate
oxidative
cleavage
reduce or
reduce, oxidise
8a-d
9a-d

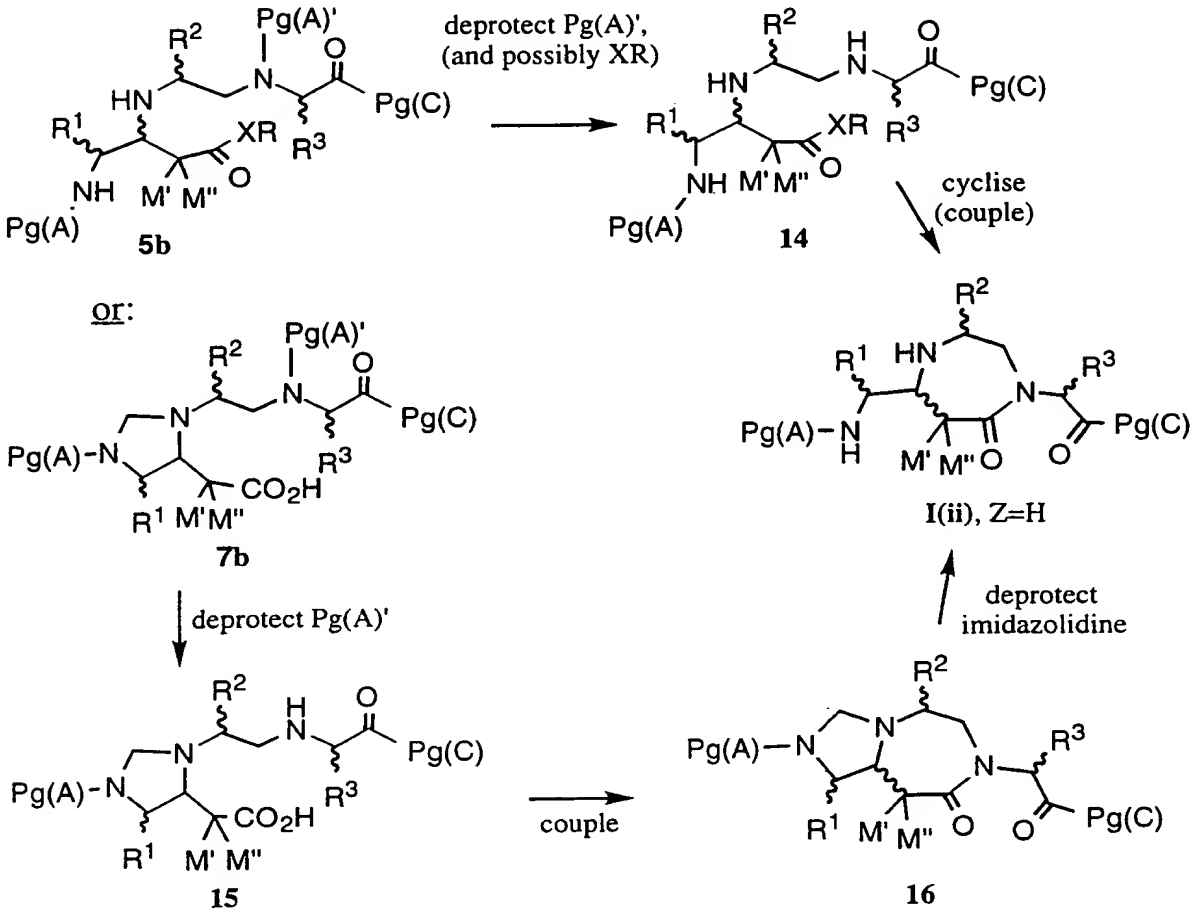
Scheme 1



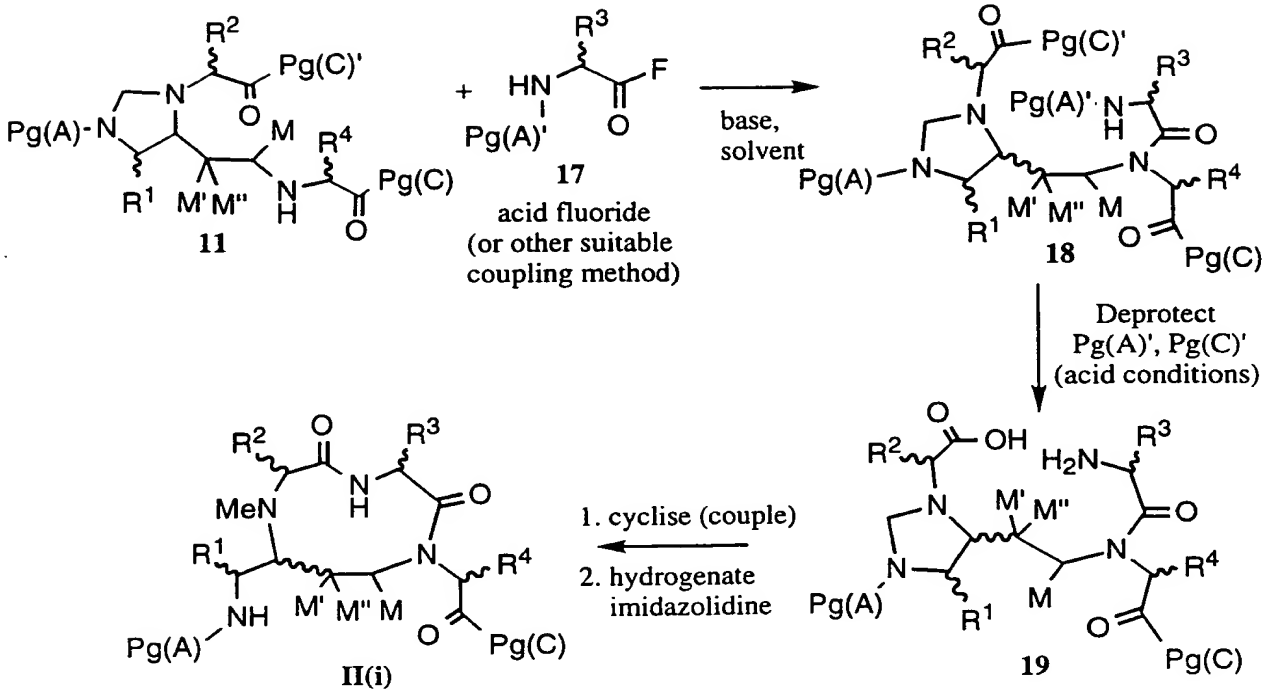
Scheme 2



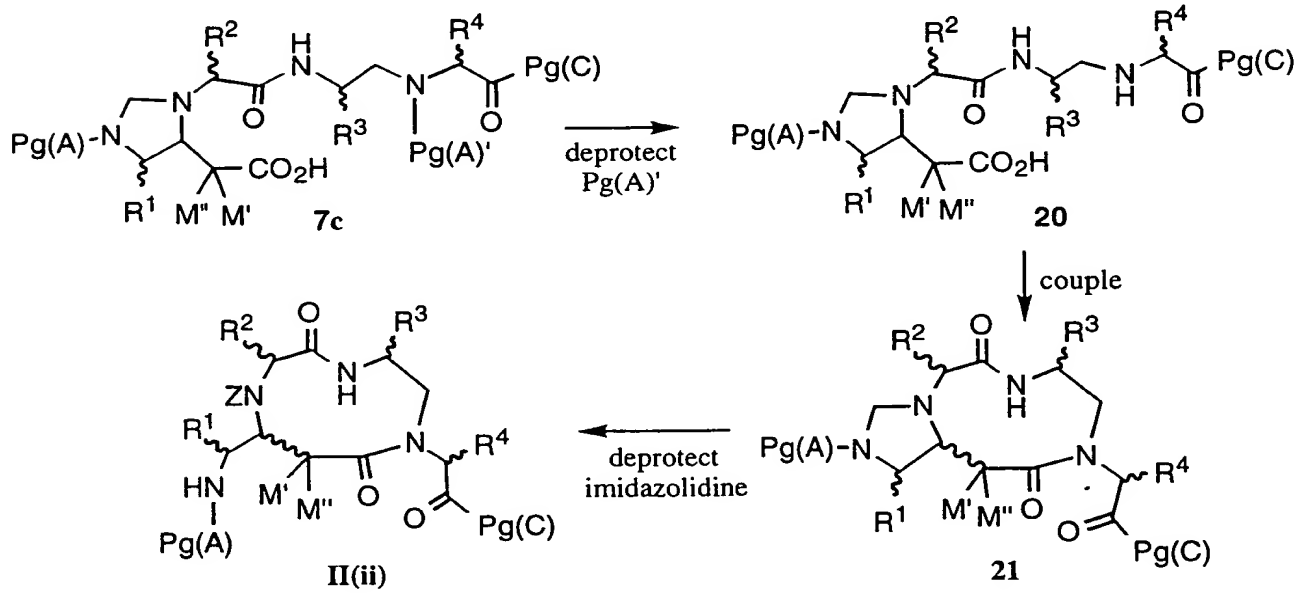
Scheme 3. Synthesis of γ-turn mimetics **I(i)**.



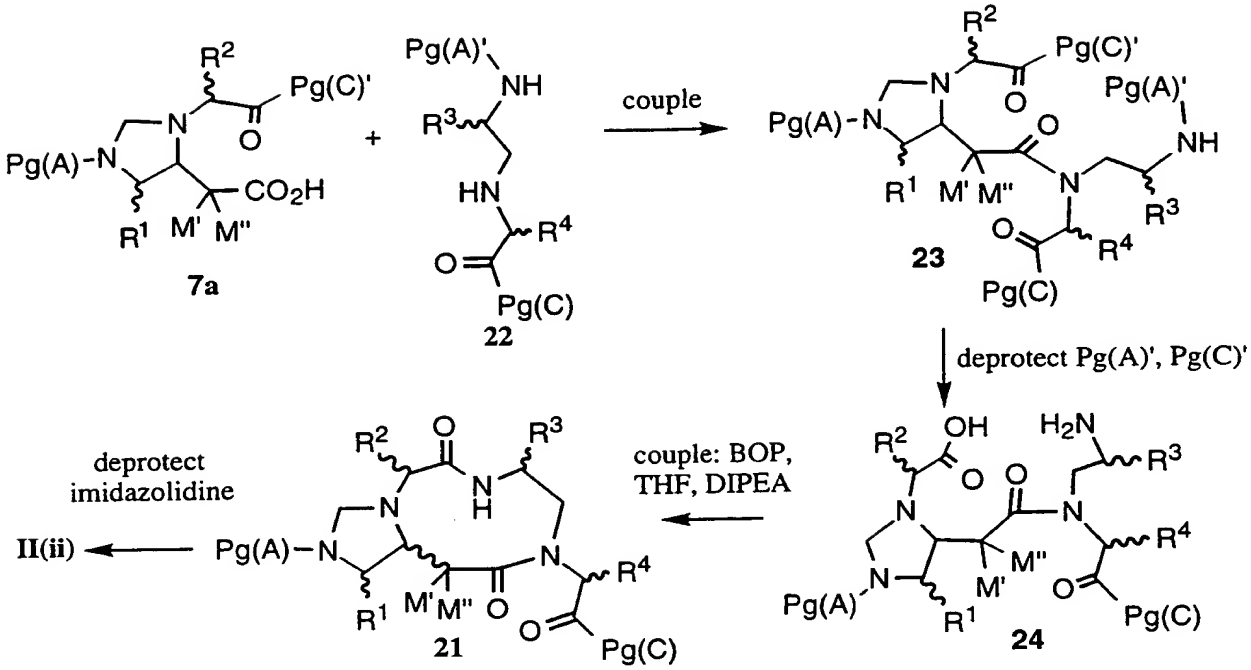
Scheme 4. Synthesis of γ-turn mimetics **I(ii)**.



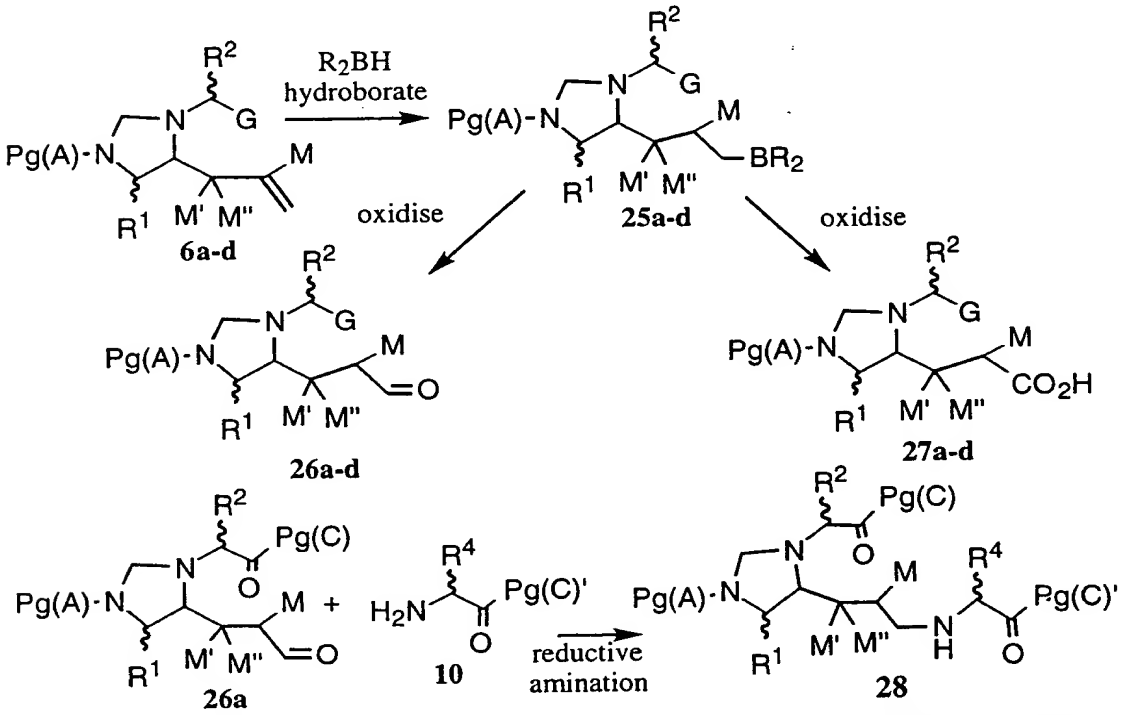
Scheme 5. Synthesis of of β-turn mimetics **II(i)**.



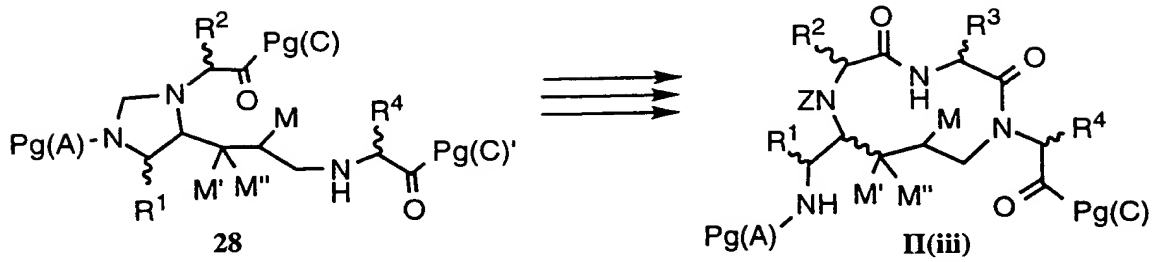
Scheme 6. Synthesis of β-turn mimetics **II(ii)**.



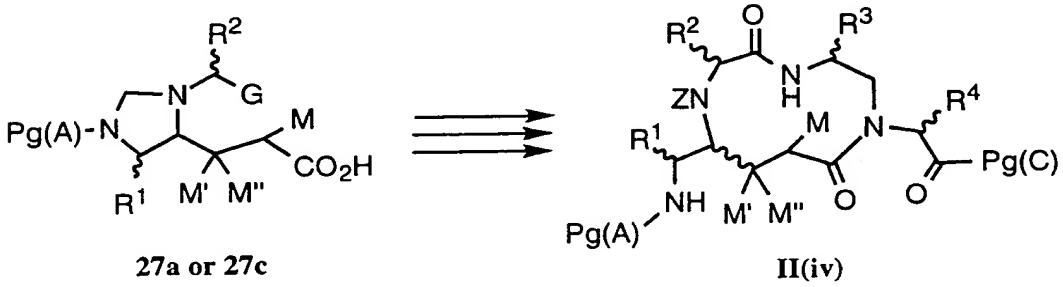
Scheme 7. Alternative synthesis of beta turn mimetics **II(ii)**



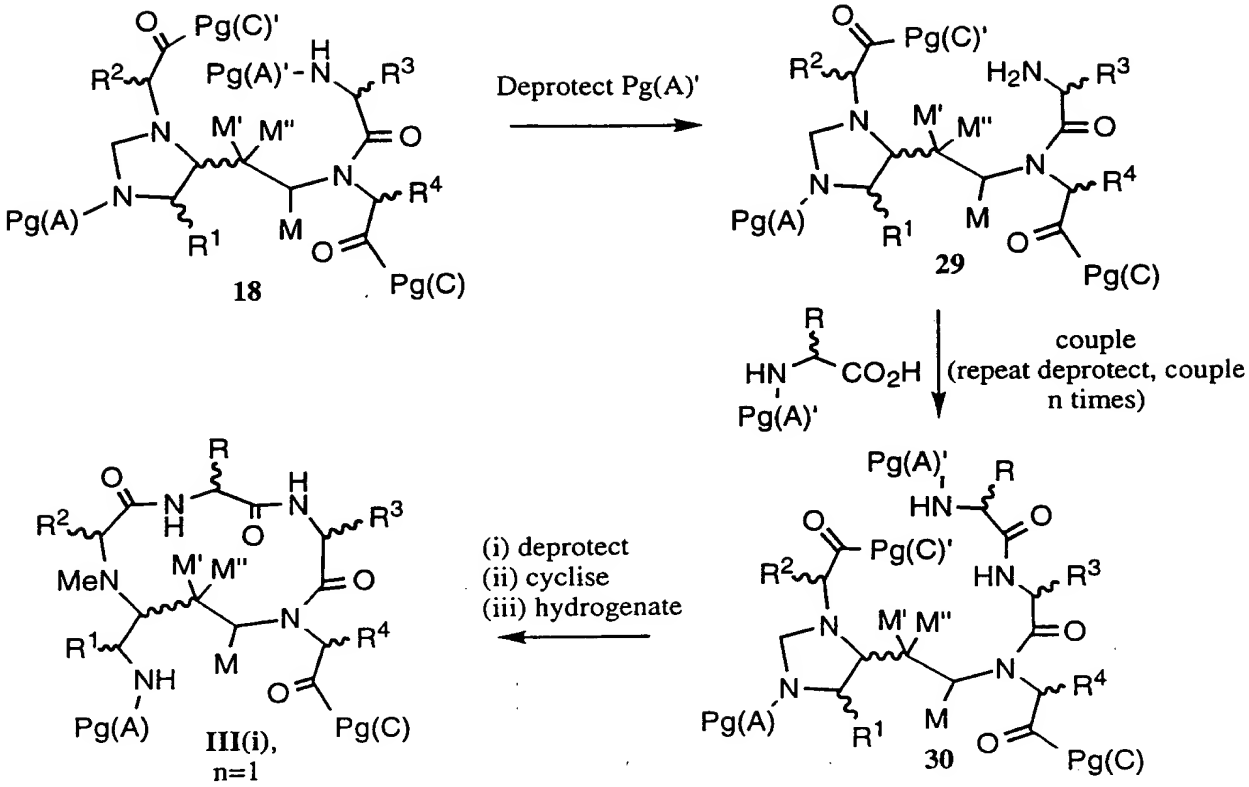
Scheme 8. General methods used in the synthesis of mimetics **II(iii)** and **II(iv)**



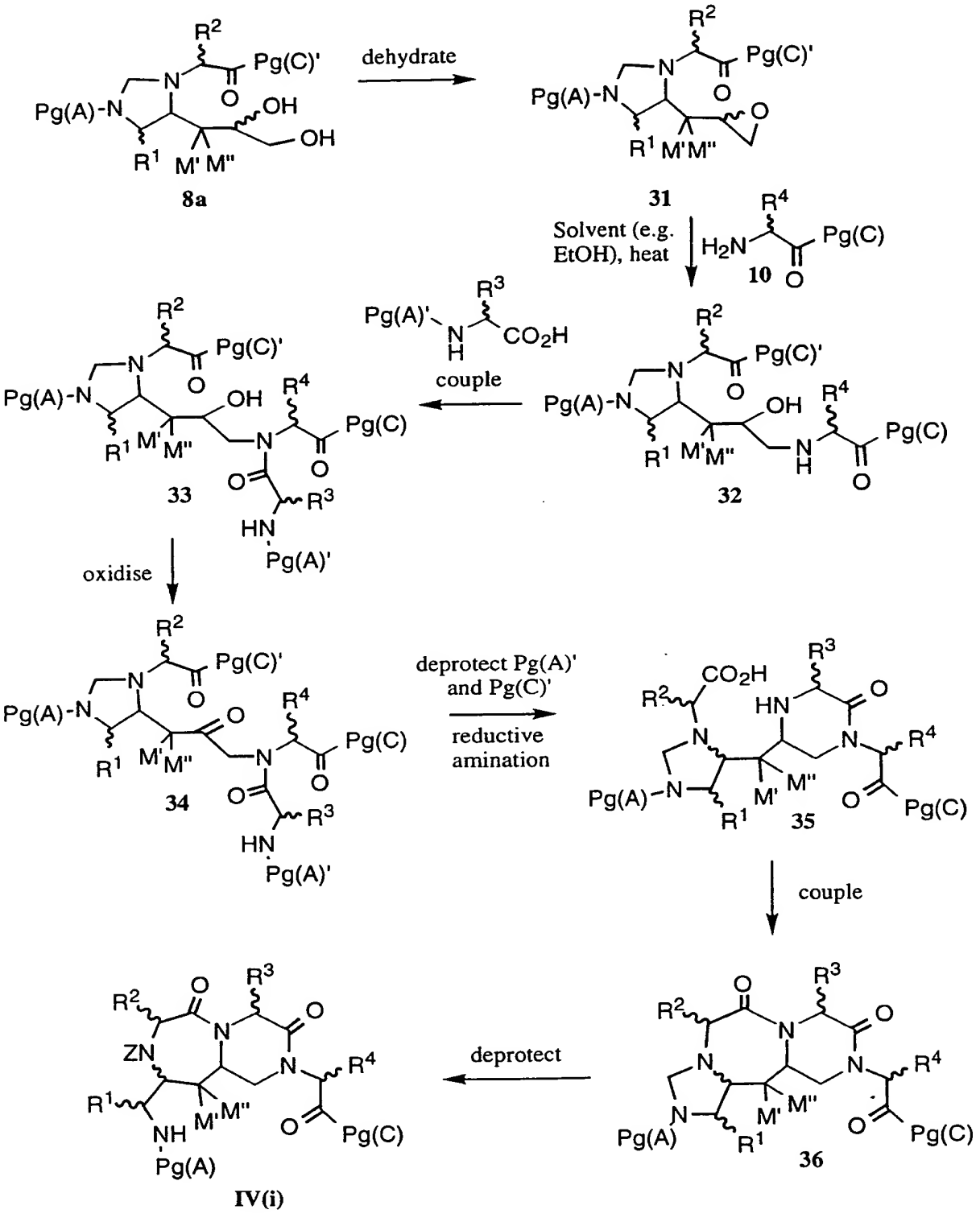
Scheme 9. Synthesis of beta turn mimetics **II(iii)**: Same as for Scheme 5, substituting **28** for **11**.



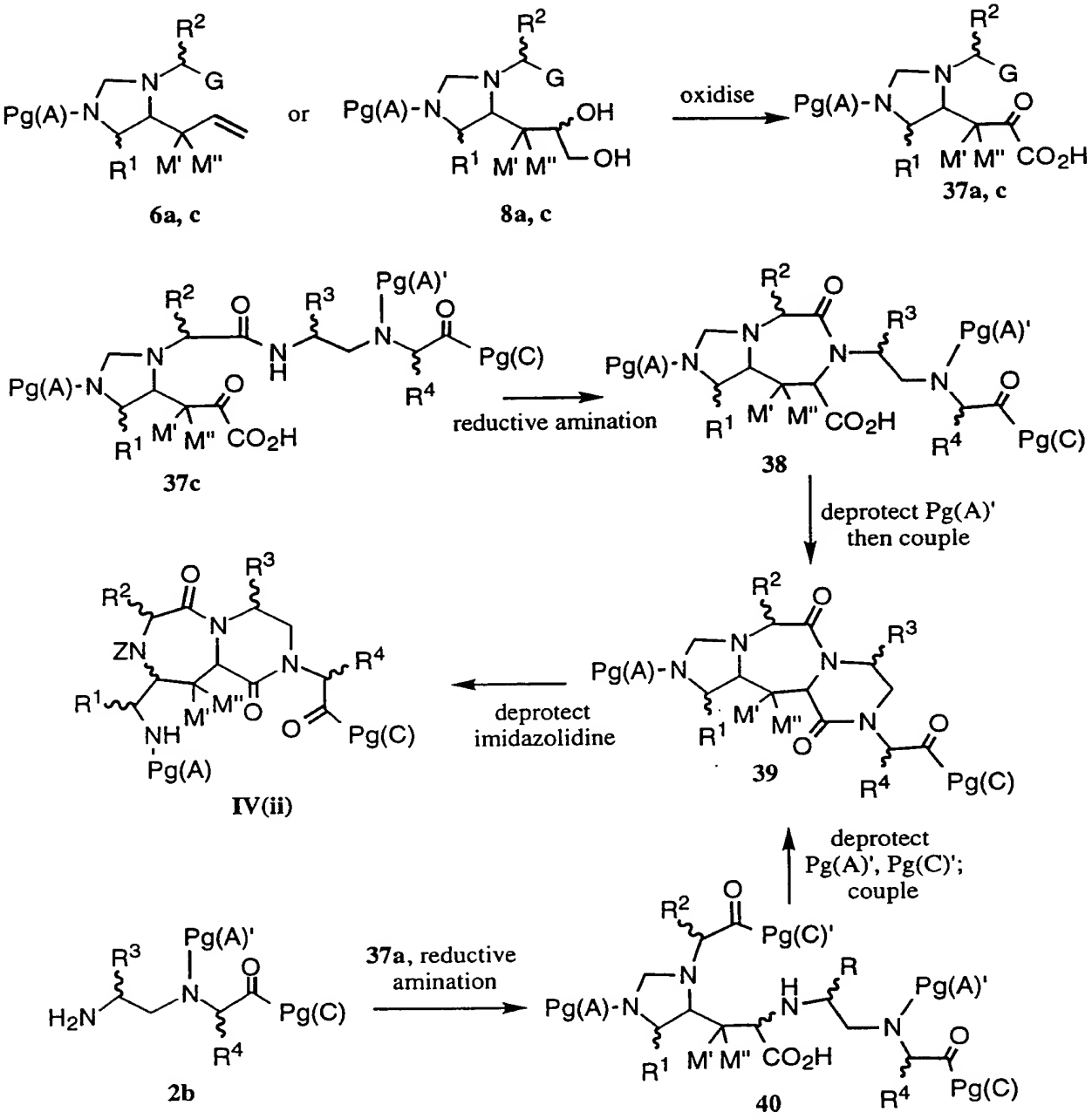
Scheme 10. Synthesis of beta turn mimetics **II(iv)**: same as Scheme 6, substituting **27c** for **7c**; alternatively, same method as for Scheme 7, substituting **27a** for **7a**.



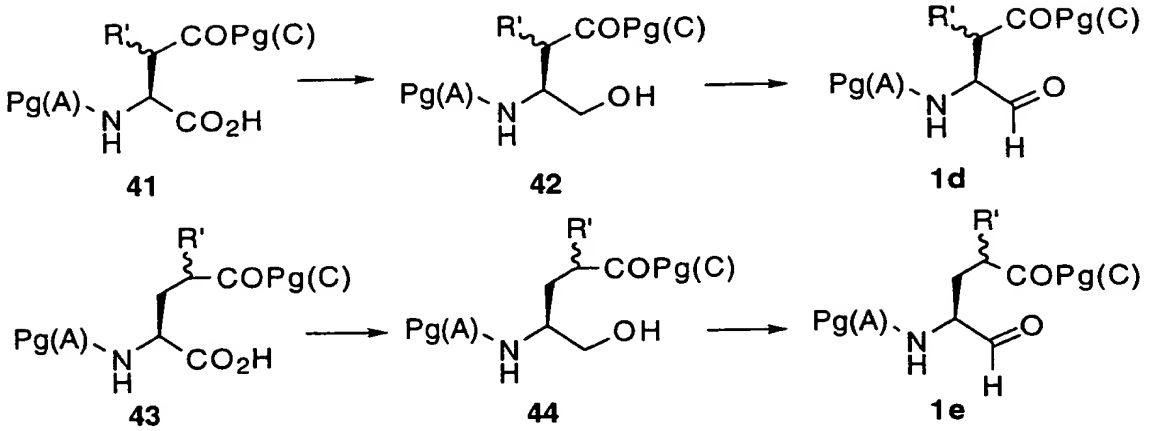
Scheme 11. Synthesis of beta buldge mimic **III(i)** using the general method for the synthesis of **II(i)** (Scheme 5).



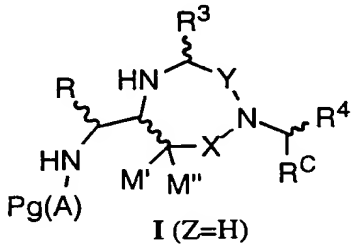
Scheme 12. Synthesis of bicyclic β-turn mimetic systems **IV(i)**.



Scheme 13. Synthesis of bicyclic beta turn mimetic systems **IV(ii)**.

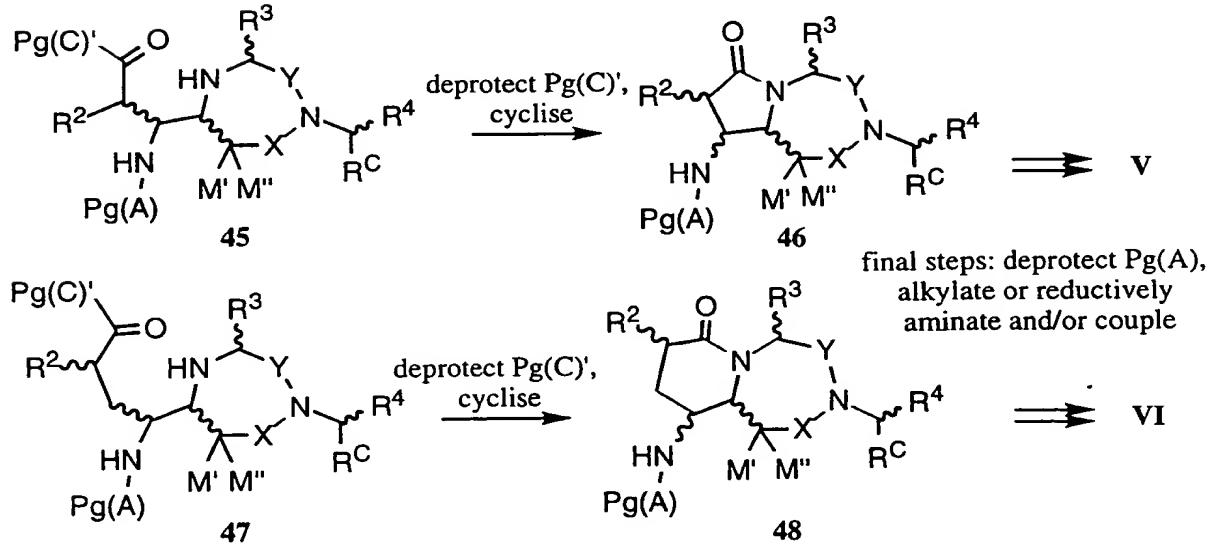


Scheme 14. Alkylated aspartic and glutamic acid derivatives

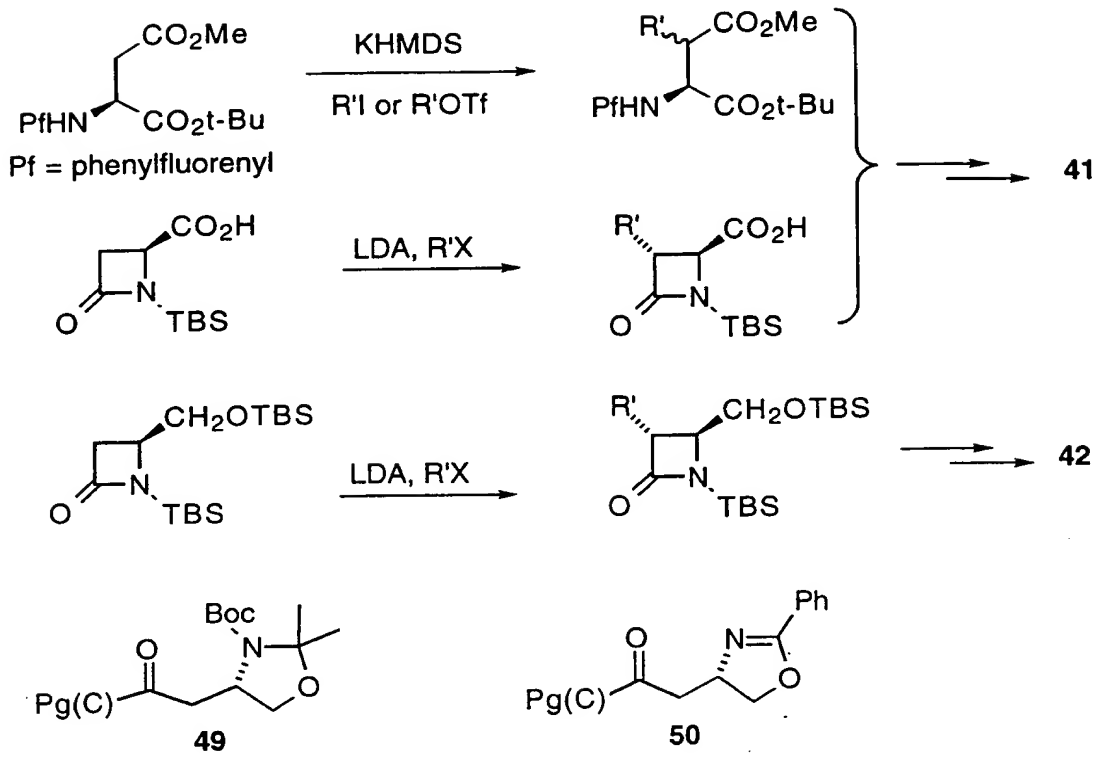


I (Z=H)

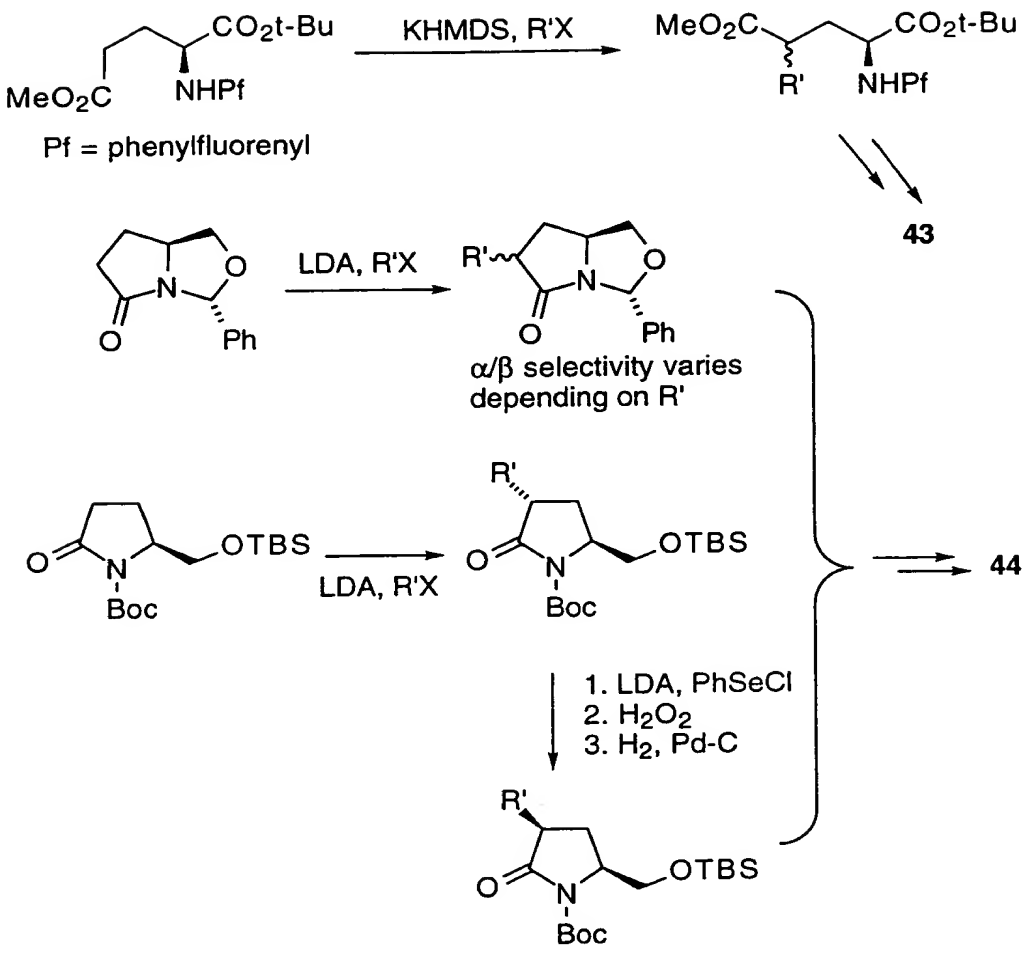
	X	Y
I(i)	CH(M)	C(O)
I(ii)	C(O)	CH_2



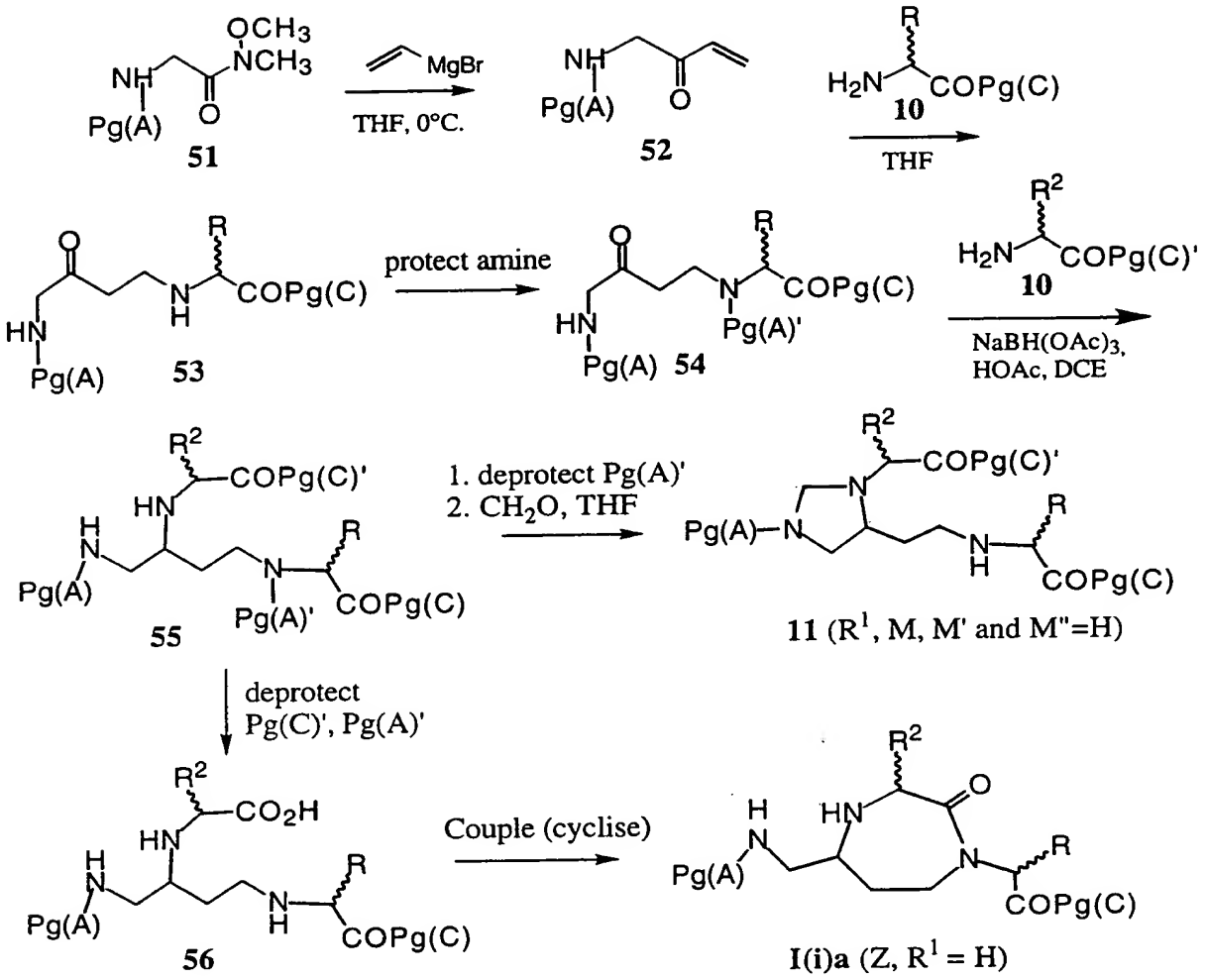
Scheme 15. Synthetic methods for the neutral bicyclic β-turn mimetics **V** and **VI**.



Scheme 16. Alkylation of aspartic acid derivatives



Scheme 17. Alkylation of glutamic acid derivatives



Scheme 18. Shorter procedure for the preparation of **11** and **I(i)a** where R^1 is hydrogen

References

Abdel-Magid, A. F., Carson, K. G., Harris, B. D., Maryanoff, C. A., & Shah, R. D. (1996). Reductive Amination of Aldehydes and Ketones with Sodium Triacetoxyborohydride. Studies on Direct and Indirect Reductive Amination Procedures. Journal of Organic Chemistry, 61, 3849-3862.

Alkorta, I., Suarez, M. L., Herranz, R., Gonzalez-Muniz, R., & Garcia-Lopez, M. T. (1996). Similarity study on peptide . gamma .- turn conformation mimetics. J. Mol. Model. [Electronic Publication], 1(Avail. URL: http://science.springer.de/molmod/1996/1_issue/mono/60020016.pdf), 16-25.

Arrhenius, T., Lerner, R. A., & Satterthwait, A. C. (1987). The chemical synthesis of structured peptides using covalent hydrogen-bond mimics. In D. Oxender (Ed.), Protein Structure, Folding and Design 2 (pp. 453-465). Alan R. Liss, Inc.

Ball, J. B., & Alewood, P. F. (1990). Conformational Constraints: Nonpeptide β-Turn Mimics. Journal of Molecular Recognition, 3(2), 55-64.

Ball, J. B., Hughes, R. A., Alewood, P. F., & Andrews, P. R. (1993). beta-Turn Topography. Tetr, 49(17), 3467-3478.

Basile, T., Bocoum, A., Savoia, D., & Umani-Ronchi, A. (1994). Enantioselective Synthesis of Homoallylic Amines by Addition of Allylmetal Reagents to Imines Derived from (S)-Valine Esters. Journal of Organic Chemistry, 59, 7766-7773.

Bernotas, R. C., & Cube, R. V. (1991). The Use of Triphenylphosphine/Diethyl azodicarboxylate (DEAD) for the Cyclisation of 1,4- and 1,5-Amino Alcohols. Tetrahedron Letters, 32(2), 161-164.

Bocoum, A., Boga, C., Savoia, D., & Umani-Ronchi, A. (1991). Diastereoselective Allylation of Chiral Imines. Novel Application of Allylcopper Reagents to the Enantioselective Synthesis of Homoallyl Amines. Tetrahedron Letters, 32, 1367-1370.

Borch, R. F., Bernstein, M. D., & Durst, H. D. (1971). The Cyanohydridoborate Anion as a Selective Reducing Agent. Journal of the American Chemical Society, 93, 2897-2904.

Boutin, R. H., & Rapoport, H. (1986). α-Amino Acid Derivatives as Chiral Educts for Asymmetric Products. Synthesis of Sphingosine from α'-Amino-α,β-ynones. Journal of Organic Chemistry, 51, 5320-5327.

Brown, H. C. (1975). Organic Syntheses Via Boranes. New York: Wiley.

Brown, H. C., & al., e. (1986). {on PCC ox. of boranes to aldehydes}. Tetrahedron, 42, 5515.

Brown, H. C., & Bhat, K. S. (1986). {allyl DIcr and aldehydes}. Journal of the American Chemical Society, 108, 293.

Brown, H. C., & Jadhav, P. K. (1983). {allyl DIP and aldehydes}. Journal of the American Chemical Society, 105, 2092.

Brown, H. C., & Jadhav, P. K. (1984). {more DIP allyl cpnds and aldehydes}. Journal of Organic Chemistry, 49, 4089.

Brown, H. C., & Krishnamurthy (1979). {selectivity of reducing agents, review}. Tetrahedron, 35, 567-607.

Brown, H. C., Kulkarni, S. U., & Rao, C. G. (1980). {PCC borane ox. to aldehydes}. Synthesis, 151.

Brown, H. C., Randad, R. S., Bhat, K. S., Zaidlewicz, M., & Racherla, U. S. (1990). {Di-isocaryl allylboranes and aldehydes}. Journal of the American Chemical Society, 112, 2389.

Callahan, J. F., Bean, J. W., Burgess, J. L., Eggleston, D. S., Hwang, S. M., Kopple, K. D., Koster, P. F., Nichols, A., Peishoff, C. E., Samanen, J. M., Vasko, J. A., Wong, A.,

& Huffman, W. F. (1992). Design and Synthesis of a C_7 Mimetic for the Predicted γ-Turn Conformation Found in Several Constrained RGD Antagonists. JMedChem, 35, 3970-3972.

Carlock, J. T., & Mack, M. P. (1978). AMild Quantitative Method For the Synthesis of a variety of heterocyclic systems. Tetrahedron Letters, 52, 5153-5156.

Carpino, L. A., El-Faham, A., & Albericio, F. (1994). Racemization studies during solid-phase peptide synthesis using azabenzotriazole-based coupling reagents. Tetrahedron Letters, 35, 2279-2280.

Carpino, L. A., Sadat-Aalaee, D., Chao, H. G., & DeSelms, R. H. (1990). FMOC amino acid fluorides. Convenient new peptide coupling reagents applicable to the FMOC/tert-butyl strategy for solution and solid phase synthesis. Journal of the American Chemical Society, 112, 9651-9652.

Chalmers, D. K., & Marshall, G. R. (1995). Pro-D-NMe-Amino Acid and D-Pro-NMe-Amino Acid: Simple, Efficient Reverse- Turn Constraints. J. Am. Chem. Soc., 117(22), 5927-37.

Chen, S., Chrusciel, R. A., Nakinishi, H., Raktabutr, A., Johnson, M. E., Sato, A., Weiner, D., Hoxie, J., Saragovi, H. U., Greene, M. I., & Kahn, M. (1992). Design and synthesis of a CD4 beta-turn mimetic that inhibits human immunodeficiency virus envelope glycoprotein gp120 binding and infection of human lymphocytes. PNAS, 89(Biochemistry), 5872-5876.

Corey, E. J. (1991). Highly enantioselective and diastereoselective synthesis of β-amino acid esters and β-lactams from achiral esters and imines. Tetrahedron Letters, 32, 5287-5290.

Cupps, T. L., Boutin, R. H., & Rapoport, H. (1985). α-Amino Acids as Chiral Educts .Journal of Organic Chemistry, 50, 3972-3979.

Ehrlich, A., Rothemund, S., Brudel, M., Beyermann, M., Carpino, L. A., & Bieneret, M. (1993). Synthesis of Cyclic Peptides via Efficient New Coupling Reagents. Tetrahedron Letters, 34, 4781-4784.

Farmer, P. S., & Ariëns, E. J. (1982). Speculations on the design of nonpeptide peptidomimetics. Topics in Peptide Science, 362-365.

Fehrentz, J.-A., & Castro, B. (1983). An Efficient Synthesis of Optically Active α-(t-Butoxycarbonylamino)-aldehydes from α-Amino Acids. SYNTHESIS, 676-678.

Frigerio, M., & Sangostino, M. (1994). A mild oxidising reagent for alcohols and 1,2-diols: o-Iodoxybenzoic Acid (IBX) in DMSO. Tetrahedron Letters, 35, 8019-8022.

Früchtel, J. S., & Jung, G. (1996). Organic Chemistry on Solid Supports. Angew. Chem. Int. Ed. Engl., 35, 17-42.

Fukuyama, Lin, & Li (1990). {reduction of thioesters to aldehydes with Et3SiH and Pd-C}. Journal of the American Chemical Society, 112, 7050.

Gallop, M. A., Barrett, R. W., Dower, W. J., Fodor, S. P. A., & Gordon, E. M. (1994). Applications of combinatorial technologies to drug discovery. 1. Background and peptide combinatorial libraries. Journal of Medicinal Chemistry, 37, 1233-1251.

Gardner, B., Nakanishi, H., & Kahn, M. (1993). Conf. Const. nonpeptide beta turn mimetics of Enkephalin. Tetr, 49(17), 3433-3448.

Giannis, A., & Kolter, T. (1993). Peptidomimetics for Receptor Ligands - Discovery, Development, and Medical Perspectives. Angew. Chem.,Int. Ed. Engl., 32, 1244-1267.

Gordon, E. M., Barrett, R. W., Dower, W. J., Fodor, S. P. A., & Gallop, M. A. (1994). Applications of combinatorial technologies to drug discovery. 2. Combinatorial organic synthesis, library screening strategies, and future directions. Journal of Medicinal Chemistry, 37, 1385-1401.

Gribble, & Nutatits (1985). {reductive amination}. Org. Prep. Proc. Int., 17, 317.

Griffith, W. P., & Ley, S. V. (1990). {tetrapropylammonium perruthenate, Pr4N+RuO4-, for oxidation of alcohols to aldehydes} TPAP. Aldrichimica Acta, 23, 13-19.
Guilbourdenche, C., Lazaro, R., Ma, S., Roumestant, M. L., Tabcheh, M. F., & Viallefont, P. (1994). Amino acids, peptides and heterocyclic chemistry. Bull. Soc. Chim. Belg., 103(1), 1-8.
Hart, D. J., & Ha, D.-C. (1989). The Ester Enolate-Imine Condensation Route to β-Lactams. Chem. Rev., 89, 1447-1465.
Henry, J. R., Marcin, L. R., McIntosh, M. C., Scola, P. M., Harris, D., Jr., & Weinreb, S. M. (1989). Mitsunobu Reactions of N-alkyl and N-acyl Sulfonamides - an efficient route to protected amines. Tetrahedron Letters, 30(42), 5709-5712.
Hirschmann, R., Nicolau, K. C., Pietranico, S., Leahy, E. M., Salvino, J., Arison, B., Cichy, M. A., Spoors, P. G., Shakespeare, W. C., Sprengler, P. A., Hamley, P., Smith III, A. B., Reisine, T., Raynor, K., Maechler, L., Donaldson, C., Vale, W., Freidinger, R. M., Cascieri, M. R., & Strader, C. D. (1993). De Novo Design and Synthesis of Somatostatin Non-Peptide Peptidomimetics Utilizing β-D-Glucose as a Novel Scaffolding. Journal of the American Chemical Society, 115, 12550-12568.
Hirschmann, R., Nicolau, K. C., Pietranico, S., Salvino, J., Leahy, E. M., Sprengler, P. A., Furst, G., Smith III, A. B., Strader, C. D., Cascieri, M. A., Candelore, M. R., Donaldson, C., Vale, W., & Maechler, L. (1992). Nonpeptidal Peptidomimetics with a beta-D-Glucose Scaffolding. A Partial Somatostatin Agonist Bearing a Close Structural Relationship to a Potent, Selective Substance P Antagonist. JACS, 114, 9217-9218.
Hirschmann, R., Yao, W., Arison, B., Maechler, L., Rosegay, A., Sprengler, P. A., & Smith, A. B., III (1996). The First Synthesis of a Tricyclic Homodetic Peptide Employing Coordinated Orthogonal Protection. Tetrahedron Letters, 37, 5637-5640.
Hölzemann, G. (1991a). Peptide Conformation Mimetics (Part 1). Kontakte (Darmstadt), 3-12.
Hölzemann, G. (1991b). Peptide Conformation Mimetics (Part 2). Kontakte (Darmstadt), 55-63.
Hudlicky, M. (1990). Oxidations in Organic Chemistry. Washington: American Chemical Society.
Huffman, W. F., Callahan, J. F., Eggleston, D. S., Newlander, K. A., Takata, D. T., Codd, E. E., Walker, R. F., Schiller, P. W., Lemieux, C., Wire, W. S., & Burks, T. F. (1988). Reverse turn mimics. In G. R. Marshall (Ed.), Peptides: Chemistry and Biology, Proceedings of the Tenth American Peptide Symposium (pp. 105-108). Leiden, The Netherlands: ESCOM.
Hughes, D. L. (1992). The Mitsunobu Reaction. Organic reactions, 42, 335-656.
Humphries, M. J., Doyle, P. M., & Harris, C. J. (1994). Integrin antagonists as modulators of cell adhesion. Exp. Opin. Ther. Patents, 4(3), 227-235.
Hutchins, R. O., & Natale, N. R. (1979). Cyanoborohydride. Utility and applications in organic synthesis. A review. Org. Prep. Proc. Int., 11, 203-241.
Jurczak, J., & Golebiowski, A. (1989). Optically Active N-Protected α-Amino Aldehydes in Organic Synthesis. Chem. Rev., 89, 149-164.
Kahn, M. (1993). Peptide Secondary Structure Mimetics: Recent Advances and Future Challanges. SYNLETT, 821-826.
Kahn, M. (1996). Library of conformationally constrained reverse- turn peptides. In64 pp. PCT Int. Appl.: Molecumetics, Ltd., USA.
Kelly, J. W., Eskew, N. L., & Evans, S. A., Jr (1986). Cyclodehydration of N- and C-Substituted 2-Amino Alcohols to the Corresponding Aziridines with Diethoxytriphenylphosphorane. Journal of Organic Chemistry, 51, 95-97.

Kessler, H., Diefenbach, B., Finsinger, D., Geyer, A., Gurrath, M., Goodman, S. L., Hölzemann, G., Haubner, R., Jonczyk, A., Müller, G., von Roedern, E. G., & Wermuth, J. (1995). Design of Superactive and Selective integrin receptor antagonists containing the RGD sequence. LIPS, 2, 155-160.

Knapp, S., Hale, J. J., Bastos, M., Molina, A., & Chen, K. Y. (1992). Synthesis of Hypusine and Other Polyamines Using Dibenzyltriazones for Amino Protection. Journal of Organic Chemistry, 57, 6239-6256.

Koskinen, A. M. P., & Rapoport, H. (1989). {γ-alkylation of N-Pf glutamic acid derivatives}. Journal of Organic Chemistry, 54, 1859-1866.

Kramer, G. W., & Brown, H. C. (1977). Organoboranes XIX. The Preparation and Some Unusual Chemistry of B-Allyl Derivatives of 9-Borabicyclo[3.3.1]nonane. Journal of Organometallic Chemistry, 132, 9-27.

Krstenansky, J. L., Baranowski, R. L., & Currie, B. L. (1982). A new approach to conformationally restricted peptide analogs: Rigid β-bends. 1. Enkephalin as an example. Biochem. Biophys. Res. Commun., 109, 1368-1374.

Kuntz, I. D. (1972). JACS, 94, 4009-4012.

Lewis, P. N., Momany, F. A., & Scheraga, H. A. (1973). Chain reversals in proteins. Biochim. Biophys. Acta, 303, 211-229.

Milner-White, E. J. (1988). One type of gamma turn rather than the other gives rise to chain reversal in proteins. Journal of Molecular Biology, 204, 777-782.

Nakanishi, H., & Kahn, M. (1996). Design of Peptidomimetics. InThe Practice of Medicinal Chemistry (pp. Ch. 27, 571-590). Academic Press Limited.

Newlander, K. A., Callahan, J. F., Moore, M. L., Tomaszek, T. A. J., & Huffman, W. F. (1993). A Novel Constrained Reduced Amide Inhibitor of HIV-1 Protease Derived from the Sequential Incorporation of .gamma.-Turn Mimetics into a Model Substrate. JMedChem, 36, 2321-2331.

Olson, G. L., Bolin, D. R., Bonner, M. P., Bös, M., Cook, C. M., Fry, D. C., Graves, B. J., Hatada, M., Hill, D. E., M, K., Madison, V. S., Rusiecki, V. K., Sarabu, R., Sepinwall, J., Vincent, G. P., & Voss, M. E. (1993). Concepts and Progress in the Development of Peptide Mimetics. Journal of Medicinal Chemistry, 36, 3039-3049.

Pelter, Smith, & Brown, H. C. (1988). Borane reagents. New York: Academic Press.

Pfister, J. R. (1984). A One Pot Synthesis of Aziridines from 2-Aminoethanols. synthesis, 969-970.

Qabar, M., Urban, J., Sia, C., Klein, M., & Kahn, M. (1996). Pharmaceutical applications of peptidomimetics. LIPS, 3, 25-30.

Ray, R., & Matteson, D. S. (1980). Osmium Tetroxide catalysed hydroxylation of hindered olefins. Tetrahedron Letters, 21, 449-450.

Richardson, J. S. (1981). The anatomy and taxonomy of protein structure. Adv. Prot. Chem., 34, 167-339.

Robinson, P. L., Barry, C. N., Bass, S. W., Jarvis, S. E., & Evans, S. A. J. (1983). Regioselective Cyclodehydration of Chiral Diols with Diethoxytriphenylphosphosphorane, Triphenylphosphine-Tetrachloromethane-Potassium Carbonate, and Triphenylphosphine-Diethyl Azodicarboxylate Reagents. A Comparitive Study. Journal of Organic Chemistry, 48, 5396-5398.

Rose, G. D., Gierasch, L. M., & Smith, J. A. (1985). Turns in peptides and proteins. Advan. Protein Chem., 37, 1-109.

Sardina, F. J., & Rapoport, H. (1996). Enantiospecific Synthesis of Heterocycles from α-Amino Acids. Chem. Rev., 96, 1825-1872.

Soderquist, J. A., & Najafi, M. R. (1986). {oxidation of boranes to alcohols using amine oxides}. Journal of Organic Chemistry, 51, 1330.

Szeja, W. (1985). {epoxides with TsCl, NaOH, BnNEt3+Cl-}. Synthesis, 983.
Valle, G., Crisma, M., Toniolo, C., Yu, K. L., & Johnson, R. L. (1989). Xtal struct. of Pro-Leu-Gly mimic peptides. International Journal of Peptide and Protein Research, 33, 181-190.
VanRheenen, V., Kelly, R. C., & Cha, D. Y. (1976). AN IMPROVED CATALYTIC OsO4 OXIDATION OF OLEFINS TO CIS-1,2-GLYCOLS USING TERTIARY AMINE OXIDES AS THE OXIDANT. Tetrahedron Letters, 23, 1973-1976.
Virgilio, A. A., & Ellman, J. A. (1994). Simultaneous Solid-Phase Synthesis of . beta .-Turn Mimetics Incorporating Side-Chain Functionality. J. Am. Chem. Soc., 116(25), 11580-1.
Virgilio, A. A., Schürer, S. C., & Ellman, J. A. (1996). Expedient solid-phase synthesis of putative β-turn mimetics incorporating the i+1, i+2, and i+3 sidechains. Tett. Lett., 37, 6961-6964.
Wenschuh, H., Beyermann, M., Krause, E., Brundel, M., Winter, R., Schümann, M., Carpino, L. A., & Bienert, M. (1994). Fmoc amino acid fluorides: Convenient reagents for the Solid Phase assembly of peptides incorporating sterically hindered residues. Journal of Organic Chemistry, 59, 3275-3280.
Wilmont, C. M., & Thornton, J. M. (1990). beta-Turns and their distortions: a proposed new nomenclature. Protein Engineering, 3, 479-493.
Wolf, J., & Rapoport, H. (1989). {β-alkylation of N-Pf aspartic acid derivatives}. Journal of Organic Chemistry, 54, 3164-3173.
Yamamoto, Y., & Asao, N. (1993). Selective Reactions of Allylic Metals. Chem. Rev., 93, 2207-2293.